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Neural Correlates of Stress-Induced and Cue-Induced Drug Craving: Influences of Sex and Cocaine Dependence

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Abstract

Objective—Although stress and drug cue exposure each increase drug craving and contribute to relapse in cocaine dependence, no previous research has directly examined the neural correlates of stress-induced and drug cue-induced craving in cocaine-dependent women and men relative to comparison subjects.

Method—Functional MRI was used to assess responses to individualized scripts for stress, drug/alcohol cue and neutral-relaxing-imagery conditions in 30 abstinent cocaine-dependent individuals (16 women, 14 men) and 36 healthy recreational-drinking comparison subjects (18 women, 18 men).

Results—Significant three-way interactions between diagnostic group, sex, and script condition were observed in multiple brain regions including the striatum, insula, and anterior and posterior cingulate. Within women, group-by-condition interactions were observed involving these regions and were attributable to relatively increased regional activations in cocaine-dependent women during the stress and, to a lesser extent, neutral-relaxing conditions. Within men, group main effects were observed involving these same regions, with cocaine-dependent men demonstrating relatively increased activation across conditions, with the main contributions from the drug and neutral-relaxing conditions. In men and women, subjective drug-induced craving measures correlated positively with corticostriatal-limbic activations.

Conclusions—In cocaine dependence, corticostriatal-limbic hyperactivity appears to be linked to stress cues in women, drug cues in men, and neutral-relaxing conditions in both. These findings suggest that sex should be taken into account in the selection of therapies in the treatment of addiction, particularly those targeting stress reduction.

While behavioral treatments are efficacious for cocaine dependence (1), relapse to cocaine use is prevalent, and stress response and stress-induced drug craving are predictive of relapse outcomes (2–4). Although stress- and drug-related stimuli produce similar stress arousal and compulsive drug-seeking responses in cocaine abusers (5), preclinical studies document important neurobiological differences in responses to stress- and drug cue-related stimuli (6) that are not well understood in humans (7, 8). Moreover, sex differences have been observed in prevalence estimates of cocaine dependence, course of illness, and treatment response (9–11). Thus, a better understanding of factors promoting drug craving

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and relapse, as well as potential sex differences in those mechanisms, could significantly benefit the development of treatments for cocaine dependence.

Cocaine-related neuroadaptations in corticostriatal-limbic circuits may underlie behavioral and cognitive aspects of cocaine dependence (12, 13). Human studies show hyporesponsivity of the anterior cingulate to behavioral tasks requiring cognitive control in cocaine abusers relative to comparison subjects (14–16). Brain activity in the amygdala, anterior cingulate, and striatum has been associated with exposure to drug-related stimuli in cocaine abusers (17–21). For example, the striatum and striatal dopamine D2/D3 receptor functioning have been associated with cue-induced drug craving and drug intake (21–24), and greater activity in the striatum is observed with increasing levels of stress (25–27). We showed previously (25) that stress exposure in cocaine-dependent individuals increases activity in the striatum, and this activation is associated with stress-induced cocaine craving. These data suggest similarities in neural responses to stress and drug cue exposure, but no study has directly compared these exposures in subjects with and without cocaine dependence.

Sex differences have been noted in brain organization, structure, chemistry, and function (28, 29). Sex hormones modulate reinforcing effects of cocaine and influence stress- and drug cue-related responses in cocaine-dependent women (10, 30–32). Sex differences in stress responses have been observed in nonaddicted and cocaine-dependent samples (33, 34). The amygdala and hippocampus, involved in emotional associative learning and memory, exhibit sex-specific differences in drug cue-related responses (29, 35). Cocaine-dependent women as compared with cocaine-dependent men show less activation of the amygdala during drug cue-induced craving (35). Sex differences have been described in dopamine pathways in striatal regions associated with instrumental learning, habits, and chronic cocaine abuse (36), and sex differences in prefrontal cortical responses to stress and reward tasks have been observed in cocaine-dependent and nonaddicted subjects (37). The insula has been implicated in cocaine cravings, at times with sex differences (20, 35, 37, 38). These data suggest that a sex-specific understanding of the neural mechanisms involved in drug craving and relapse risk is warranted in order to develop more effective treatments for addictions.

In this study, we directly investigated the main and interactive influences of diagnostic group (with and without cocaine dependence), sex, and cue state (stress, drug-related, neutral-relaxing) on regional brain activation, thus allowing the comparison of neural activity during stress- and drug cue-induced craving states and neutral-relaxing states in individuals with and without cocaine dependence, as well as assessment of the role of sex in these responses. We utilized a well-established, individualized-script-driven imagery paradigm that has been used in previous studies of cocaine dependence and other psychiatric disorders (see reference 39 for a review). Based on previous neuroimaging research, our hypotheses addressed corticostriatal-limbic circuits involved in emotion, stress, and motivation. We hypothesized that we would observe a three-way interaction of sex, diagnostic group, and cue condition with respect to corticostriatal-limbic activation. Given the data summarized above, we hypothesized that this three-way interaction would involve cocaine-dependent women showing greater corticostriatal activation to stress cues than comparison women and cocaine-dependent men showing greater activation to drug/alcohol cues than comparison men. We also hypothesized that among cocaine-dependent women, subjective measures of stress-induced craving would correlate positively with stress cue condition-related corticostriatal-limbic activation and that among cocaine-dependent men, subjective measures of drug-induced craving would correlate positively with drug cue condition-related corticostriatal-limbic activation.

Method

Participants

Thirty cocaine-dependent patients between the ages of 21 and 50 years participated in the study. Cocaine-dependent patients were treatment-seeking on admission and treatment-engaged while residing on a locked inpatient research unit and participating in treatment there for at least 2 weeks before functional MRI (fMRI) scanning. Inclusion criteria included a current diagnosis of cocaine dependence as determined by the Structured Clinical Interview for DSM-IV (40) and weekly self-reported use of cocaine before admission as verified by urine toxicology. Individuals who met criteria for DSM-IV dependence on a substance other than alcohol or tobacco were excluded. Thirty-six comparison subjects (18 of them women) participated. Comparison subjects were free of psychiatric disorders, were of similar age to the cocaine-dependent group, and were not hospitalized. All comparison subjects reported recreational alcohol consumption (an average of six drinks per week) and had never met criteria for abuse or dependence. Comparison subjects had not consumed alcohol for at least 72 hours before scanning.

The study was approved by the Yale Human Investigations Committee, and all participants provided written informed consent.

Imagery Script Development

Individualized scripts for stress, drug/alcohol cue, and neutral-relaxing conditions were generated in structured clinical interview sessions using scene development questionnaires, as described previously (25, 37). Two stress, two substance cue, and two neutral-relaxing scripts were developed for each participant. The substance cue scripts involved cocaine for cocaine-dependent subjects and alcohol for comparison subjects. Stress and neutral-relaxing scripts did not involve substance-related material. Each stress situation was individually calibrated by the participant using a 10-point Likert scale ranging from 1 (“least stressful”) to 10 (“most stressful”), and only items that were rated 8 or above were selected for script development. Sample scripts are provided in the data supplement that accompanies the online edition of this article.

fMRI Acquisition and Analysis

Images were obtained using a 3-T Siemens Trio MRI system equipped with a standard quadrature head coil, using T_2*-sensitive gradient-recalled single shot echo planar pulse sequence and analyzed as described previously (25) and in the online data supplement. The AFNI software package (http://afni.nimh.nih.gov/afni) was used for whole-brain random-effects analysis (41) to investigate the hypothesized three-way interaction of sex, diagnostic group, and script condition as described in the online data supplement. To identify sources of the identified three-way interaction, main and interactive effects were investigated using 2×3 analyses of variance (ANOVAs) in men and women separately. To identify sources of the interactive and main effects of the within-sex ANOVAs, comparisons between cocaine-dependent and comparison subjects were investigated for each script condition in men and women separately.

Whole-brain correlational analyses, in which individual activation patterns were correlated with self-report ratings of stress-induced craving in the stress condition and drug-induced craving in the drug cue condition, using the neutral condition as a comparison condition (as has been done previously [20]), were examined in men and women separately. Analyses were conducted in BioImageSuite with application of AFNI AlphaSim family-wise error correction for multiple comparisons set at $p<0.05$ (two-tailed) (42, 43).

Subjective and Physiological Measures

Subjective measures of craving and anxiety, along with recorded heart rate, were assessed using mixed-effects models (PROC MIXED) in SAS, version 9.0 (SAS Institute, Cary, N.C.). Main effects and interactions for group, sex, and cue condition were assessed. Significant interactions were examined further using simple effects to understand sources of interactions.

Results

Thirty cocaine-dependent patients (16 of them women) and 36 comparison subjects (18 of them women) participated in the study (Table 1). There were no significant between-group differences in race or age between male and female cocaine-dependent and comparison subjects. Cocaine-dependent patients had less education on average than comparison subjects and reported more cocaine and alcohol use. Cocaine-dependent women and men reported similar recent and chronic use of cocaine and similar lengths of abstinence before scanning.

Subjective and Physiological Responses

Consistent with previous studies (5, 37, 44), a main effect of condition was observed for anxiety ($F=66.15$, $df=2, 124$, $p<0.0001$), craving ($F=37.09$, $df=2, 124$, $p<0.0001$), and heart rate ($F=4.14$, $df=2, 122$, $p=0.02$). In each case, responses were higher for the stress and drug/alcohol cue conditions as compared with the neutral-relaxing one (p values, <0.0001) (see Figure S1A–F in the online data supplement). Significant group main effects and group-by-condition interactions were observed for anxiety (group: $F=7.25$, $df=1, 62$, $p<0.009$; group-by-condition: $F=8.95$, $df=2, 124$, $p=0.0002$) and craving (group: $F=25.14$, $df=1, 62$, $p<0.0001$; group-by-condition: $F=12.21$, $df=2, 124$, $p<0.0001$), with cocaine-dependent patients relative to comparison subjects reporting greater increases for craving ($p<0.0001$) and anxiety ($p<0.0001$) in the drug cue condition (see Figure S1A–B). No significant main or interaction effects of sex were observed.

Influences of Sex, Diagnostic Group, and Cue Condition on Brain Activations

A three-way interaction of sex, diagnostic group, and cue condition was observed with respect to corticostriatal-limbic activations in the striatum, insula, and anterior and posterior cingulate cortices (Table 2; see also Figure S2 in the online data supplement). To investigate the nature of the three-way interactions, main and interaction effects were examined in women and men separately.

Influences of diagnostic group and cue condition on brain activation in women

In women, a robust main effect of condition involving a diffuse network of corticostriatal-limbic circuitry was observed (see Figure S3A and Table S1B in the online data supplement). A main effect of diagnostic group identified the lateral and medial ventral prefrontal cortices, ventral striatum, and insula (see Figure S4A and Table S2A in the online data supplement). An interaction between diagnostic group and cue condition was observed in a broader network involving the lateral and medial ventral prefrontal cortices, ventral striatum, insula, anterior and posterior cingulate, temporal and parietal cortices, and dorsomedial and dorsolateral prefrontal cortices (see Figure S4B and Table S2B in the online data supplement).

Between-group differences by cue condition in women

To examine the nature of the main and interactive effects related to diagnostic group and cue condition in women, between-group contrasts for each condition were examined. Of the

three conditions, the most diffuse and robust differences were observed for the stress comparison, in which cocaine-dependent women showed greater activation than comparison women in the amygdala, hippocampus, lateral and medial ventral prefrontal cortices, ventral and dorsal striatum, insula, anterior cingulate, temporal and parietal cortices, and dorsomedial and dorsolateral prefrontal cortices (Figure 1; see also Figure S5A and Table S3A–i in the online data supplement). Cocaine-dependent women showed greater activation than comparison women during the neutral-relaxing condition in the medial and lateral ventral and dorsal prefrontal cortices and in the ventral striatum (Figure 1; see also Figure S5B and Table S3A–ii in the online data supplement). In contrast, the cocaine-dependent women showed less brain activation than comparison women during the drug/alcohol cue condition in the posterior cingulate, dorsal frontal, and parietal cortices (Figure 1; see also Figure S5C and Table S3A–iii in the online data supplement).

Secondary analyses to explore whether effects varied in women being tested in the follicular versus luteal phases of the cycle were also conducted. No family-wise-error-corrected between-phase brain activation differences were observed in either cocaine-dependent or comparison women.

Influences of diagnostic group and cue condition on brain activation in men— As in women, a robust main effect of cue condition involving a diffuse network of corticostriatal-limbic circuitry was observed in men (see Figure S3B and Table S1C in the online data supplement). In contrast to the findings in women, the main effect of diagnostic group analysis identified a broader network of regions (the lateral and medial ventral prefrontal cortices, ventral striatum, insula, anterior and posterior cingulate, temporal and parietal cortices, and dorsomedial and dorsolateral prefrontal cortices) (see Figure S4C and Table S2C in the online data supplement), whereas the group-by-condition interaction identified fewer regions (the posterior cingulate and parietal cortices) (see Figure S4D and Table S2D in the online data supplement).

Between-group differences by cue condition in men—Across the drug and neutral-relaxing conditions, cocaine-dependent men relative to comparison men showed increased activation in the amygdala; hippocampus; ventral and lateral prefrontal cortices; insula; ventral and dorsal striatum; thalamus; anterior and posterior cingulate, temporal, and parietal cortices; and dorsolateral and dorsomedial prefrontal cortices (Figure 1; see also Figure S5E–F and Table S3A–v–vi in the online data supplement), with increased activation seen in a more restricted subset of these regions (the striatum, thalamus, and temporal cortex) during the stress condition (Figure 1; see also Figure S5D and Table 3B–iv in the online data supplement). Relatively decreased activation in the precuneus was seen in the stress condition (Figure 1; see also Figure S5D and Table S3A–iv in the online data supplement).

Associations Between Regional Brain Activations and Subjective Craving

Given sex differences in the neural correlates of stress-and drug-induced craving response, we investigated separately in cocaine-dependent women and men correlations between subjective measures of craving and brain activations. In women, subjective craving elicited during the drug cue condition correlated positively with brain activations in the drug cue-versus-neutral-condition contrast in the midbrain, hippocampus, ventrolateral prefrontal cortex, temporal cortex, cerebellum, and thalamus (see Figure S6A and Table S3B–i in the online data supplement). In women, subjective craving elicited during the stress condition did not correlate with brain activations in the stress-versus-neutral-condition contrast at a whole-brain-corrected level.

Among cocaine-dependent men, subjective craving elicited during the drug cue condition correlated positively with brain activations in the contrast of drug cue versus neutral condition in the hippocampus, insula, posterior cingulate, dorsolateral and dorsomedial prefrontal cortices, temporal and parietal cortices, and cerebellum (see Figure S6B and Table S3B–ii in the online data supplement). In men, subjective craving elicited during the stress condition correlated with brain activations in the contrast of stress versus neutral condition in the cerebellum and parietal cortices (see Figure S6C and Table S3B–iii in the online data supplement).

Discussion

To our knowledge, this is the first study to systematically investigate sex differences in the subjective, physiological, and neural correlates of both stress-induced and cue-induced craving in cocaine dependence. Given the differential associations between these two types of craving and treatment outcome (2), the findings have significant clinical implications. A more precise understanding of similarities and differences in the biological correlates of stress-induced and cue-induced craving in cocaine-dependent women and men will help identify targets for treatment development and lead to improved therapies. The inclusion of a recreational-drinking comparison group facilitated the identification of neural correlates of stress- and cue-related craving that are specific to pathological involvement in substance use behaviors. The clinical implications of the identification of sex-related influences on neural activations related to stress- and drug cue-related craving are described below.

Subjective and Physiological Measures

Consistent with previous studies (25, 37, 39, 44), the script-driven guided imagery method successfully elicited subjective distress and drug craving. Robust main and interactive effects of cue condition and diagnostic group on self-reported craving and anxiety were observed as expected: stress and drug cue conditions (as compared with the neutral-relaxing condition) were associated with greater subjective anxiety and craving, with stronger craving reported in cocaine-dependent patients than in recreational drinkers, consistent with previous findings (5). A main effect of condition was observed on heart rate, a finding driven by the least change in the neutral-relaxing condition as compared with elevations in the stress and drug cue conditions. However, no main or interactive effect of diagnostic group was observed on heart rate. Arguably most significantly, and as in several (33, 45) but not all (46, 47) previous investigations of sex differences in physiological responses in cocaine-dependent subjects, no main or interactive influences of sex were observed on self-report or heart rate measures. These findings highlight the importance of exploring alternative methodologies such as brain imaging to understand clinically relevant sex differences related to stress and drug responsiveness in cocaine-dependent and comparison subjects.

Brain Activations

Consistent with our first hypothesis, a three-way interaction of sex, diagnostic group, and script condition involving corticostriatal-limbic circuitry was observed. Our hypothesis that this interaction would involve cocaine-dependent women showing greater corticostriatal-limbic activation relative to comparison women during the stress condition was also supported, although this pattern of increased corticostriatal-limbic activation extended to the neutral-relaxing condition, albeit to a lesser degree. Also consistent with our hypothesis, cocaine-dependent men showed greater corticostriatal-limbic activation relative to comparison men during the substance cue condition. However, in men, cocaine-dependent status was associated to a greater degree with increased corticostriatal-limbic activation across conditions, an effect particularly evident during the drug cue and neutral-relaxing

conditions. These differences in brain activation patterns during stress and drug cue conditions in cocaine-dependent men and women cannot be explained by current mood or anxiety ratings, as there were no sex differences in these scores. Thus, these findings suggest that corticostriatal-limbic hyperactivity may be particularly linked to stress cues in cocaine-dependent women and drug cues in cocaine-dependent men, with both cocaine-dependent groups also showing corticostriatal-limbic hyperactivity during neutral-relaxing conditions.

Areas identified as showing overactivation in cocaine-dependent women but not in cocaine-dependent men during the stress condition include the amygdala, hippocampus, insula, anterior cingulate, and ventromedial, ventrolateral, dorsomedial, and dorsolateral prefrontal cortices, regions implicated in emotional regulation, memory function, interoceptive processing, cognitive control, and emotional and motivational processing (48–50). Areas identified as being overactive in cocaine-dependent men during the drug condition overlap substantially with those that were overactive in cocaine-dependent women during the stress condition, suggesting that similar neural circuits are responsive to varying degrees in different environmental contexts (stress for women, drug cues for men) for the drug-seeking behavior of cocaine-dependent women and men.

Both similarities and differences were observed in neural responses to stress and drug cues in cocaine-dependent women and men. In men, between-group differences during the stress condition involved predominantly increased activation in the striatum, thalamus, and temporal cortex, regions involved in stress responsiveness, motivation, and auditory processing (48, 51), and these differences were also seen in women, suggesting an effect of cocaine dependence across the sexes.

Although mainly hyperactivation was observed in cocaine-dependent subjects, hypoactivated regions warrant consideration. During the stress condition, cocaine-dependent men showed relatively diminished activation of the precuneus, a region implicated in attention and impulse control and showing relatively less activation in cocaine abusers during sustained attention (52, 53). Thus, stress in cocaine-dependent men may interfere with the ability to attend to and control behavior in part through poor recruitment of the precuneus. Analogously, during the substance cue condition, cocaine-dependent women relative to comparison women showed less activation in predominantly dorsal and cortical brain regions, including the inferior parietal lobule, precuneus, and posterior cingulate, suggesting that drug cues in women may interfere with recruitment of attentional processing and impulse control regions.

The relatively increased activation of corticostriatal-limbic circuitry during the neutral-relaxing condition in cocaine-dependent subjects is noteworthy. In cocaine-dependent women, this hyperreactivity involved the ventral striatum, ventromedial prefrontal cortex, lateral orbitofrontal cortex, and inferior frontal gyrus, regions implicated in motivation, reward processing, decision making, and impulse control (49, 54, 55). These regions were also overactive in cocaine-dependent men during the neutral-relaxing condition, as were the amygdala, hippocampus, insula, and anterior and posterior cingulate cortices, regions implicated in emotional regulation, memory function, interoceptive processing, cognitive control, and emotional and motivational processing (48–50). The neutral-relaxing condition served as a nonspecific control condition and is associated with decreases in negative emotion and increases in relaxation and positive emotional responses (56, 57). In previous studies, cocaine-dependent subjects showed less relaxation and lower positive emotion during neutral-relaxed states relative to comparison subjects (5), and abstinent, treatment-engaged cocaine-dependent individuals showed higher subjective, behavioral, and physiological responses to stress at baseline and in response to stress, drug cue, and neutral-relaxing imagery exposure (4, 5, 31, 33). In light of our findings in the present study, this

higher baseline distress state in cocaine-dependent subjects appears to be represented as hyperreactivity in the corticostriatal-limbic circuitry during neutral-relaxing imagery.

Correlations With Subjective Craving

Our hypotheses regarding correlations with self-reported craving were partially supported. Consistent with our hypothesis, correlations in men between drug cue-related craving and corticostriatal-limbic activation were observed and involved the hippocampus, insula, and anterior and posterior cingulate, consistent with previous findings (19, 20, 35, 58). Drug cue-related cravings in cocaine-dependent women also positively correlated with corticostriatal-limbic activation in the hippocampus, insula, orbitofrontal cortex, putamen, and midbrain regions. However, in contrast to our hypothesis, no significant correlations between stress-related brain activations and stress cue-related cravings in cocaine-dependent women survived whole-brain correction, whereas those in men implicated the cerebellum and parietal cortices, regions previously associated with subjective craving, albeit to cocaine cues (58), and particularly in women (35). Taken together, the more diffuse correlations between drug cue-related craving and brain activations suggest that subjective drug cue-related craving may be more closely linked to a broader activation of corticostriatal-limbic circuitry than are stress cue-related subjective responses. Furthermore, the similarities between men and women in neural correlates of drug cue-related craving are consistent with preclinical and clinical studies of cocaine self-administration, chronic cocaine exposure, and drug craving that show similarities across sexes in corticostriatal-limbic contributions (13, 59, 60).

Clinical Implications

Our findings have several clinical implications. First, they suggest that regional brain activation responses during provoked stress cue states in women, drug cue states in men, and neutral-relaxing states in both might serve as neural markers in evaluating the efficacy of new behavioral and pharmacological treatments for cocaine dependence (8, 61, 62). Direct investigation of this hypothesis (e.g., by using this paradigm in conjunction with clinical trials) is warranted. Second, increased corticostriatal-limbic activity during stress, particularly in cocaine-dependent women, suggests the importance of teaching stress reduction, perhaps with mindfulness techniques (63, 64), in order to decrease hyperresponsiveness of corticostriatal-limbic regions and restore the brain’s ability to discriminate between relevant and irrelevant stimuli and sharpen adaptive and regulatory responses that rely on such information. Given the increased stress cue-related neural activations in cocaine-dependent women in conjunction with an absence of significant neural correlations with subjective responses, techniques to increase patients’ ability to utilize contextual cues to identify emotion and improve learning and memory abilities may help during emotional processing and in regulation of emotions and craving states. The observed increased corticostriatal-limbic activity during the drug cue condition in cocaine-dependent men suggests that training to manage exposure or responses to drug cues, through 12-step or cognitive-behavioral approaches, may be particularly helpful for men. The observed increased corticostriatal-limbic activity during the neutral-relaxing state in cocaine-dependent subjects, and particularly men, suggests the importance of exploring methods for decreasing basal corticostriatal-limbic activation, perhaps through mindfulness meditation or exercise.

Strengths, Limitations, and Future Directions

We used a large, well-defined sample to investigate the neural correlates of stress- and drug cue-related craving in cocaine-dependent and comparison subjects. A strength of the study lies in the whole-brain analytic approach used to assess neural activity. Limitations include possible susceptibility artifacts during fMRI and the potential for cues to have lingering

subjective or neural effects. Specific design and analytic approaches (e.g., pre-fMRI training in progressive relaxation, relaxation components following each cue, counterbalancing of cue presentation orders, inclusion of baseline neural response as a regressor in analyses) were used to diminish lingering influences. Frequent tobacco smoking was observed among cocaine-dependent subjects. Although imaging findings persisted after correcting for smoking and other differences (e.g., in education level), future studies should examine the potential influence of tobacco use and other individual differences (e.g., in emotional dysregulation) on stress, drug cue, and neutral-relaxing responses. Although there were no sex differences in unprovoked craving measures during early abstinence (days 1 and 4 after admission), future studies should examine subjective and neural correlates of stress- and drug cue-induced craving at different stages of addiction. Although our exploratory analysis did not find a significant influence of menstrual cycle phase in the group and condition effects in women, the sample sizes for women in each phase were small. Future research should examine the influence of sex hormones on the neural correlates of craving. As this study is the first to examine interactive effects of sex and cocaine dependence on neural responses to both stress and drug/alcohol cue exposure, its identification of clinically relevant sex differences has important implications for treatment development.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Carroll KM, Onken LS. Behavioral therapies for drug abuse. Am J Psychiatry. 2005; 162:1452–1460. [PubMed: 16055766]
2. Sinha R, Garcia M, Paliwal P, Kreek MJ, Rounsaville BJ. Stress-induced cocaine craving and hypothalamic-pituitary-adrenal responses are predictive of cocaine relapse outcomes. Arch Gen Psychiatry. 2006; 63:324–331. [PubMed: 16520439]
3. McKay JR, Lynch KG, Pettinati HM, Shepard DS. An examination of potential sex and race effects in a study of continuing care for alcohol- and cocaine-dependent patients. Alcohol Clin Exp Res. 2003; 27:1321–1323. [PubMed: 12966329]
4. Sinha R. The role of stress in addiction relapse. Curr Psychiatry Rep. 2007; 9:388–395. [PubMed: 17915078]
5. Fox HC, Hong KI, Siedlarz K, Sinha R. Enhanced sensitivity to stress and drug/alcohol craving in abstinent cocaine-dependent individuals compared to social drinkers. Neuropsychopharmacology. 2008; 33:796–805. [PubMed: 17568398]
6. Shaham Y, Hope BT. The role of neuroadaptations in relapse to drug seeking. Nat Neurosci. 2005; 8:1437–1439. [PubMed: 16251983]
7. O'Brien CP. Anticraving medications for relapse prevention: a possible new class of psychoactive medications. Am J Psychiatry. 2005; 162:1423–1431. [PubMed: 16055763]

8. Sinha R, Li CS. Imaging stress- and cue-induced drug and alcohol craving: association with relapse and clinical implications. Drug Alcohol Rev. 2007; 26:25–31. [PubMed: 17364833]
9. Brady K, Back S, McRae A. Gender differences in response to HPA axis response in drug-dependent individuals: implications for psychiatric comorbidity. J Womens Health. 2007; 16:1108.
10. Lynch WJ, Roth ME, Carroll ME. Biological basis of sex differences in drug abuse: preclinical and clinical studies. Psychopharmacology. 2002; 164:121–137. [PubMed: 12404074]
11. Nich C, McCance-Katz EF, Petrakis IL, Cubells JF, Rounsaville BJ, Carroll KM. Sex differences in cocaine-dependent individuals' response to disulfiram treatment. Addict Behav. 2004; 29:1123–1128. [PubMed: 15236812]
12. Goldstein RZ, Alia-Klein N, Tomasi D, Zhang L, Cottone LA, Maloney T, Telang F, Caparelli EC, Chang L, Ernst T, Samaras D, Squires NK, Volkow ND. Is decreased prefrontal cortical sensitivity to monetary reward associated with impaired motivation and self-control in cocaine addiction? Am J Psychiatry. 2007; 164:43–51. [PubMed: 17202543]
13. Porrino LJ, Smith HR, Nader MA, Beveridge TJ. The effects of cocaine: a shifting target over the course of addiction. Prog Neuropsychopharmacol Biol Psychiatry. 2007; 31:1593–1600. [PubMed: 17900777]
14. Kaufman J, Ross TJ, Stein EA, Garavan H. Cingulate hypoactivity in cocaine users during a go-nogo task as revealed by eventrelated functional magnetic resonance imaging. J Neurosci. 2003; 23:7839–7843. [PubMed: 12944513]
15. Hester R, Fassbender C, Garavan H. Individual differences in error processing: a review and reanalysis of three event-related fMRI studies using the go/nogo task. Cereb Cortex. 2004; 14:986–994. [PubMed: 15115734]
16. Li CS, Huang C, Yan P, Bhagwagar Z, Milivojevic V, Sinha R. Neural correlates of impulse control during stop signal inhibition in cocaine-dependent men. Neuropsychopharmacology. 2008; 33:1798–1806. [PubMed: 17895916]
17. Childress AR, Mozley PD, McElgin W, Fitzgerald J, Reivich M, O'Brien CP. Limbic activation during cue-induced cocaine craving. Am J Psychiatry. 1999; 156:11–18. [PubMed: 9892292]
18. Garavan H, Pankiewicz J, Bloom A, Cho J-K, Sperry L, Ross TJ, Salmeron BJ, Risinger R, Kelley D, Stein EA. Cue-induced cocaine craving: neuroanatomical specificity for drug users and drug stimuli. Am J Psychiatry. 2000; 157:1789–1798. [PubMed: 11058476]
19. Wexler BE, Gottschalk CH, Fulbright RK, Prohovnik I, Lacadie CM, Rounsaville BJ, Gore JC. Functional magnetic resonance imaging of cocaine craving. Am J Psychiatry. 2001; 158:86–95. [PubMed: 11136638]
20. Kilts C, Schweitzer JB, Quinn CK, Gross RE, Faber TL, Muhammad F, Ely TD, Hoffmann JM, Drexler KPG. Neural activity related to drug craving in cocaine addiction. Arch Gen Psychiatry. 2001; 58:334–341. [PubMed: 11296093]
21. Volkow ND, Wang GJ, Telang F, Fowler JS, Logan J, Childress AR, Jayne M, Ma Y, Wong C. Cocaine cues and dopamine in dorsal striatum: mechanism of craving in cocaine addiction. J Neurosci. 2006; 26:6583–6588. [PubMed: 16775146]
22. Heinz A, Siessmeier T, Wrase J, Buchholz HG, Gründer G, Kumakura Y, Cumming P, Schreckenberger M, Smolka MN, Rösch F, Mann K, Bartenstein P. Correlation of alcohol craving with striatal dopamine synthesis capacity and $D_{2/3}$ receptor availability: a combined [^{18}F]DOPA and [^{18}F]DMFP PET study in detoxified alcoholic patients. Am J Psychiatry. 2005; 162:1515–1520. [PubMed: 16055774]
23. Wong DF, Kuwabara H, Schretlen DJ, Bonson KR, Zhou Y, Nandi A, Brasic JR, Kimes AS, Maris MA, Kumar A, Contoreggi C, Links J, Ernst M, Rousset O, Zukin S, Grace AA, Lee JS, Rohde C, Jasinski DR, Gjedde A, London ED. Increased occupancy of dopamine receptors in human striatum during cue-elicited cocaine craving. Neuropsychopharmacology. 2006; 31:2716–2727. [PubMed: 16971900]
24. Martinez D, Kim JH, Krystal J, Abi-Dargham A. Imaging the neurochemistry of alcohol and substance abuse. Neuroimaging Clin N Am. 2007; 17:539–555. [PubMed: 17983969]
25. Sinha R, Lacadie C, Skudlarski P, Fulbright RK, Rounsaville BJ, Kosten TR, Wexler BE. Neural activity associated with stress-induced cocaine craving: a functional magnetic resonance imaging study. Psychopharmacology (Berl). 2005; 183:171–180. [PubMed: 16163517]

26. Oswald LM, Wong DF, Zhou Y, Kumar A, Brasic J, Alexander M, Ye W, Kuwabara H, Hilton J, Wand GS. Impulsivity and chronic stress are associated with amphetamine-induced striatal dopamine release. Neuroimage. 2007; 36:153–166. [PubMed: 17433881]
27. Pruessner JC, Champagne F, Meaney MJ, Dagher A. Dopamine release in response to a psychological stress in humans and its relationship to early life maternal care: a positron emission tomography study using [11C]raclopride. J Neurosci. 2004; 24:2825–2831. [PubMed: 15028776]
28. Sinha, R. Sex differences in brain fMRI responses to stress, in Biology of Personality and Individual Differences. Canli, T., editor. New York: Guilford; 2006. p. 203-222.
29. Cahill L. Why sex matters for neuroscience. Nature Rev Neurosci. 2006; 7:477–491. [PubMed: 16688123]
30. Sofuoglu M, Dudish-Poulsen S, Nelson D, Pentel PR, Hatsukami DK. Sex and menstrual cycle differences in the subjective effects from smoked cocaine in humans. Exp Clin Psychopharmacol. 1999; 7:274–283. [PubMed: 10472516]
31. Fox HC, Hong KA, Paliwal P, Morgan PT, Sinha R. Altered levels of sex and stress steroid hormones assessed daily over a 28-day cycle in early abstinent cocaine-dependent females. Psychopharmacology (Berl). 2008; 195:527–536. [PubMed: 17891383]
32. Sinha R, Fox H, Hong KI, Sofuoglu M, Morgan PT, Bergquist KT. Sex steroid hormones, stress response, and drug craving in cocaine-dependent women: implications for relapse susceptibility. Exp Clin Psychopharmacol. 2007; 15:445–452. [PubMed: 17924778]
33. Fox HC, Garcia M, Kemp K, Milivojevic V, Kreek MJ, Sinha R. Gender differences in cardiovascular and corticoadrenal response to stress and drug cues in cocaine dependent individuals. Psychopharmacology (Berl). 2006; 185:348–357. [PubMed: 16514523]
34. Kajantie E, Phillips DI. The effects of sex and hormonal status on the physiological response to acute psychosocial stress. Psychoneuroendocrinology. 2006; 31:151–178. [PubMed: 16139959]
35. Kilts CD, Gross RE, Ely TD, Drexler KPG. The neural correlates of cue-induced craving in cocaine-dependent women. Am J Psychiatry. 2004; 161:233–241. [PubMed: 14754771]
36. Munro CA, McCaul ME, Wong DF, Oswald LM, Zhou Y, Brasic J, Kuwabara H, Kumar A, Alexander M, Ye W, Wand GS. Sex differences in striatal dopamine release in healthy adults. Biol Psychiatry. 2006; 59:966–974. [PubMed: 16616726]
37. Li C-S, Kosten TR, Sinha R. Sex differences in brain activation during stress imagery in abstinent cocaine users: a functional magnetic resonance imaging study. Biol Psychiatry. 2005; 57:487–494. [PubMed: 15737663]
38. Bonson K, Grant SJ, Contoreggi CS, Links JM, Metcalfe J, Weyl L, Kurian V, Ernst M, London ED. Neural systems and cue-induced cocaine craving. Neuropsychopharmacology. 2002; 26:376–386. [PubMed: 11850152]
39. Sinha R. Modeling stress and drug craving in the laboratory: implications for addiction treatment development. Addict Biol. 2009; 14:84–98. [PubMed: 18945295]
40. First, MB.; Spitzer, RL.; Williams, JBW.; Gibbon, M. Structured Clinical Interview for DSM-IV–Patient Edition (SCID-P). Washington, DC: American Psychiatric Press; 1995.
41. Cox RW. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. Comput Biomed Res. 1996; 29:162–173. [PubMed: 8812068]
42. Papademetris, X.; Jackowski, M.; Rajeevan, N.; Constable, RT.; Staib, LH. BioImage Suite: An Integrated Medical Image Analysis Suite. New Haven, Yale School of Medicine, Department of Diagnostic Radiology, Section of Bioimaging Sciences; 2006. (http://www.bioimagesuite.org)
43. Seo D, Jia Z, Lacadie CM, Tsou KA, Bergquist K, Sinha R. Sex differences in neural responses to stress and alcohol cues. Hum Brain Mapp. 2011; 32:1998–2013. [PubMed: 21162046]
44. Sinha R, Talih M, Malison R, Anderson GA, Cooney N, Kreek M. Hypothalamic-pituitary-adrenal axis and sympatho-adreno-medullary responses during stress-induced and drug cueinduced cocaine craving states. Psychopharmacology (Berl). 2003; 170:62–72. [PubMed: 12845411]
45. Robbins S, Ehrman RN, Childress AR, O'Brien CP. Comparing levels of cocaine cue reactivity in male and female outpatients. Drug Alcohol Depend. 1999; 53:223–230. [PubMed: 10080048]
46. McCance-Katz EF, Hart CL, Boyarsky B, Kosten T, Jatlow P. Gender effects following repeated administration of cocaine and alcohol in humans. Subst Use Misuse. 2005; 40:511–528. [PubMed: 15830733]

47. Back SE, Brady KT, Jackson JL, Salstrom S, Zinzow H. Gender differences in stress reactivity among cocaine-dependent individuals. Psychopharmacology (Berl). 2005; 180:169–176. [PubMed: 15682303]
48. Li CS, Sinha R. Inhibitory control and emotional stress regulation: neuroimaging evidence for frontal-limbic dysfunction in psycho-stimulant addiction. Neurosci Biobehav Rev. 2008; 32:581–597. [PubMed: 18164058]
49. Koob GF, Volkow ND. Neurocircuitry of addiction. Neuropsychopharmacology. 2010; 35:217–238. [PubMed: 19710631]
50. Naqvi NH, Bechara A. The hidden island of addiction: the insula. Trends Neurosci. 2009; 32:56–67. [PubMed: 18986715]
51. Everitt B, Robbins TW. Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. Nat Neurosci. 2005; 8:1481–1489. [PubMed: 16251991]
52. Castellanos FX, Margulies DS, Kelly C, Uddin LQ, Ghaffari M, Kirsch A, Shaw D, Shehzad Z, Di Martino A, Biswal B, Sonuga-Barke EJ, Rotrosen J, Adler LA, Milham MP. Cingulate-precuneus interactions: a new locus of dysfunction in adult attention-deficit/ hyperactivity disorder. Biol Psychiatry. 2008; 63:332–337. [PubMed: 17888409]
53. Goldstein RZ, Tomasi D, Alia-Klein N, Zhang L, Telang F, Volkow ND. The effect of practice on a sustained attention task in cocaine abusers. Neuroimage. 2007; 35:194–206. [PubMed: 17236790]
54. Hampshire A, Chamberlain SR, Monti MM, Duncan J, Owen AM. The role of the right inferior frontal gyrus: inhibition and attentional control. Neuroimage. 2010; 50:1313–1319. [PubMed: 20056157]
55. Clark L. Decision-making during gambling: an integration of cognitive and psychobiological approaches. Phil Trans Royal Society B. 2010; 365:319–330.
56. Sinha R, Fuse T, Aubin LR, O'Malley SS. Psychological stress, drug-related cues, and cocaine craving. Psychopharmacology (Berl). 2000; 152:140–148. [PubMed: 11057517]
57. Chaplin TM, Hong K, Bergquist K, Sinha R. Gender differences in response to emotional stress: an assessment across subjective, behavioral, and physiological domains and relations to alcohol craving. Alcohol Clin Exp Res. 2008; 32:1242–1250. [PubMed: 18482163]
58. Grant S, London ED, Newlin DB, Villemagne VL, Liu X, Contoreggi C, Phillips RL, Kimes AS, Margolin A. Activation of memory circuits during cue-elicited cocaine craving. Proc Nat Acad Sci USA. 1996; 93:12040–12045. [PubMed: 8876259]
59. Beveridge TJ, Smith HR, Nader MA, Porrino LJ. Abstinence from chronic cocaine self-administration alters striatal dopamine systems in rhesus monkeys. Neuropsychopharmacology. 2009; 34:1162–1171. [PubMed: 18769473]
60. See RE, Elliott JC, Feltenstein MW. The role of dorsal vs ventral striatal pathways in cocaine-seeking behavior after prolonged abstinence in rats. Psychopharmacology (Berl). 2007; 194:321–331. [PubMed: 17589830]
61. Volkow ND, Fowler JS, Wang GJ, Swanson JM, Telang F. Dopamine in drug abuse and addiction: results of imaging studies and treatment implications. Arch Neurol. 2007; 64:1575–1579. [PubMed: 17998440]
62. Brewer JA, Worhunsky PD, Carroll KM, Rounsaville BJ, Potenza MN. Pretreatment brain activation during Stroop task is associated with outcomes in cocaine-dependent patients. Biol Psychiatry. 2008; 64:998–1004. [PubMed: 18635157]
63. Brewer JA, Sinha R, Chen JA, Michalsen RN, Babuscio TA, Nich C, Grier A, Bergquist KL, Reis DL, Potenza MN, Carroll KM, Rounsa ville BJ. Mindfulness training reduces stress reactivity and relapse in substance abuse: results from a randomized, controlled pilot study. Subst Abus. 2009; 30:306–317. [PubMed: 19904666]
64. Brewer JA, Smith JT, Bowen S, Marlatt GA, Potenza MN. Applying mindfulness-based treatments to co-occurring depression and substance use disorders: what can we learn from the brain? Addiction. 2010; 105:1698–1706. [PubMed: 20331548]

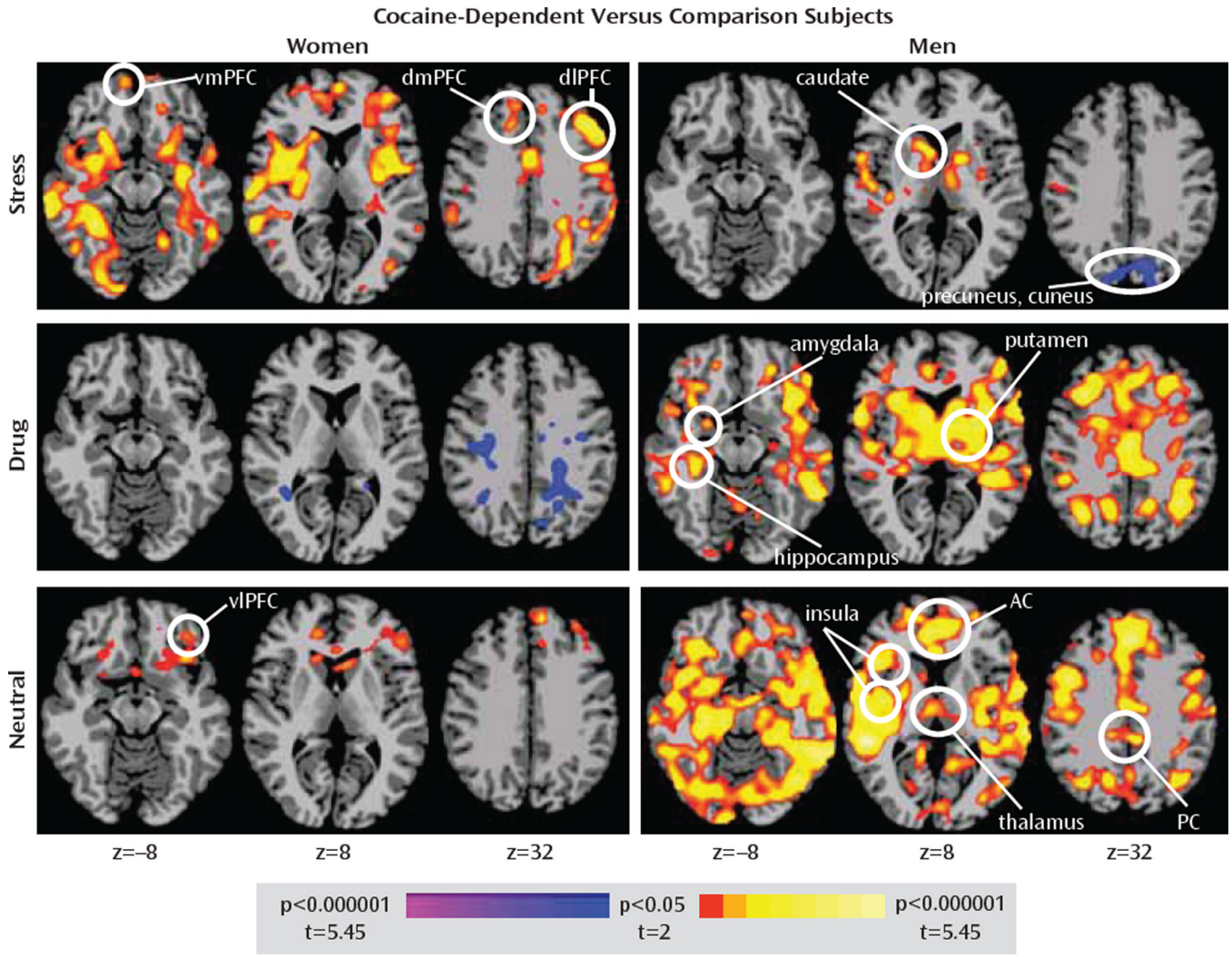

FIGURE 1. Brain Activation Maps for Cocaine-Dependent and Comparison Women and Men in Three Cue Conditionsa

[a]Images show between-diagnostic-group contrast maps highlighting regions where cocaine-dependent patients showed more activation than comparison subjects (in yellow to red color) and regions where cocaine-dependent patients showed less activation than comparison subjects (in blue to purple color) during the stress, drug, and neutral-relaxing cue conditions for women and men. Maps are thresholded at $p<0.05$, with a family-wise error correction. Color bars indicate the magnitudes of between-group differences. Regions are selectively labeled to highlight key findings. AC=anterior cingulate cortex; dlPFC=dorsolateral prefrontal cortex; dmPFC=dorsomedial prefrontal cortex; PC=posterior cingulate cortex; vlPFC=ventrolateral prefrontal cortex; vmPFC=ventromedial prefrontal cortex.

TABLE 1

Demographic and Clinical Characteristics of Cocaine-Dependent and Comparison Women and Men in a Study of Stress- and Cue-Induced Craving

Characteristic	Cocaine-Dependent Group				Comparison Group				Analysis Statistic	df	p
	Female (N=16)		Male (N=14)		Female (N=18)		Male (N=18)				
	N	%	N	%	N	%	N	%	χ^2		
Caucasian	7	43.7	7	50.0	8	44.4	11	61.1	1.3	3	0.73
Current tobacco smoker	13	81.2	11	78.6	2	11.1	3	16.7	29.2	3	<0.0001
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F		
Age (years)	36.9	6.4	35.9	5.2	31.2	8.8	33.4	9.8	1.75	3	0.17
Education (years)	12.6	1.1	12.1	1.8	15.1	2.1	14.7	2.2	10.28	3	<0.0001
Cocaine use (days/past 30 days)	20.2	9.1	18.1	8.9	0	0	0	0	2.25[a]	1	0.14
Alcohol use (days/past 30 days)	12.1	9.2	8.7	8.3	2.2	3.0	6.0	7.1	5.87	3	0.002
Years of cocaine use	8.4	6.7	11.3	6.5	0	0	0	0	1.38[a]	1	0.25
Years of alcohol use	11.9	6.3	15.75	8.0	4.5	4.7	14.0	10	6.36	3	0.0009
Days in hospital prior to fMRI (days)	23.3	5.7	22.3	3.0	0	0	0	0	1.38[a]	0.32	0.58

[a]For cocaine-dependent sample only.

TABLE 2

Three-Way Interaction of Sex, Diagnostic Group, and Cue Condition in Cocaine-Dependent and Comparison Women and Men in a Study of Stress- and Cue-Induced Craving[a]

Region	Volume (mm^3)	Volume (Voxels)	Talairach Coordinates			Mean t	SD
			x	y	z		
Right insula, hippocampus, amygdala, putamen, and Brodmann areas 38 and 20	15,437	572	37	−7	−9	3.75	0.57
Right Brodmann areas 38 and 20	3,773	140	32	−3	−26	3.88	0.68
Right putamen	1,748	65	27	−10	0	3.57	0.40
Right amygdala, hippocampus	2,078	77	27	−4	−12	3.79	0.44
Right insula	3,557	132	37	3	3	3.49	0.32
Right Brodmann area 44	1,666	62	49	10	2	3.70	0.45
Right Brodmann area 22	2,615	97	36	−3	−8	4.03	0.69
Caudate, anterior cingulate, and Brodmann areas 47 and 46	19,802	733	−20	31	6	3.90	0.64
Left Brodmann area 10	8,175	303	−30	41	18	3.94	0.72
Left and right caudate, ventral striatum	4,027	149	1	17	−2	3.81	0.55
Left Brodmann area 45	4,430	164	−28	34	6	3.94	0.59
Left Brodmann area 46	2,321	86	−44	38	6	3.99	0.64
Left anterior cingulate	849	31	−13	40	14	3.59	0.35
Posterior cingulate and Brodmann areas 39 and 7	63,152	2339	8	−51	35	4.16	0.93
Left Brodmann area 6	11,571	429	−19	−6	50	4.30	1.20
Right Brodmann area 21, fusiform, Brodmann area 19	15,787	585	41	−54	−2	3.85	0.67

[a]The table lists the results of the family-wise error whole brain corrected voxel-based analyses ($p<0.05$) for the three-way interaction of sex, diagnostic group (with and without cocaine dependence), and cue condition (stress, drug/alcohol-related, and neutral-relaxing).