Published in final edited form as:

Am J Drug Alcohol Abuse. 2016 September ; 42(5): 577–586. doi:10.1080/00952990.2016.1192183.

Attenuated neural response to emotional cues in cocaine-dependence: a preliminary analysis of gender differences

Melanie Canterberry, PhD^a, MacKenzie R. Peltier, PhD^{a,b}, Kathleen T. Brady, MD, PhD^{a,c}, and Colleen A. Hanlon, PhD^a

^aDepartment of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, SC, USA

^bDepartment of Psychology, Louisiana State University, Baton Rouge, LA, USA

^cRalph H. Johnson VA Medical Center, Charleston, SC, USA

Abstract

Background—Cocaine users often report a loss of arousal for nondrug-related stimuli, which may contribute to their response to drug-related rewards. However, little is known about users' neural reactivity to emotional nondrug-related stimuli and the potential influence of gender.

Objectives—Test the hypotheses that cocaine-dependent individuals have an attenuated neural response to arousing stimuli relative to controls and that this difference is amplified in women.

Methods—The brain response to typically arousing positive and negative images as well as neutral images from the International Affective Picture System was measured in 40 individuals (20 non-treatment seeking cocaine-dependent and 20 age- and gender-matched control participants; 50% of whom were women). Images were displayed for 4 s each in blocks of five across two 270-second runs. General linear models assessed within and between group activation differences for the emotional images.

Results—Cocaine-dependent individuals had a significantly lower response to typically arousing positive and negative images than controls, with attenuated neural activity present in the medial prefrontal cortex (mPFC) and anterior cingulate cortex (ACC). Analyses by gender revealed less mPFC/ACC activation among female users, but not males, for both positive and negative images.

Conclusion—The dampened neural response to typically arousing stimuli among cocaine-dependent polydrug users suggests decreased salience processing for nondrug stimuli, particularly among female users. This decreased responding is consistent with data from other substance using populations and suggests that this may be a general feature of addiction. Amplifying the neural

CONTACT Colleen A. Hanlon, PhD, hanlon@musc.edu, Department of Psychiatry, Medical University of South Carolina, 67 President Street, Room 502 North, Charleston, SC 29425, USA.

ORCID

Colleen A. Hanlon <http://orcid.org/0000-0002-3151-0279>

Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/iada.

Supplemental data for this article can be accessed on the publisher's website.

Declaration of interest

The authors declare no conflicts of interest.

response to naturally arousing nondrug-related reinforcers may present an opportunity for unique behavioral and brain stimulation therapies.

Keywords

Cocaine; emotion; fMRI; addiction; gender

Background

Although decision-making and emotional arousal are often treated independently in scientific literature, it is known that emotional reactivity to salient stimuli is a critical element to future decision-making (1). An individual's response to natural rewards (e.g., food, sex, and social bonding) and negative stimuli (e.g., infant cries, threats to relationships, or personal safety) promotes survival as well as physical and mental well-being. Cocaine-dependent individuals often report difficulty experiencing nondrug-related rewards (anhedonia) and continue drug use despite potential negative outcomes (2). Cocaine users are relatively insensitive to the rewarding aspects of emotionally salient positive stimuli which promote survival, such as sex and infant cues (3–5).

Viewing emotionally salient stimuli typically leads to elevated activity in a network of prefrontal and subcortical brain regions, including the medial prefrontal cortex (mPFC), anterior cingulate cortex (ACC), ventral and dorsal striatum, and amygdala (6,7). These brain regions are involved with salience detection, affective processing, and motivated behavior. Substance-dependent individuals typically have less cue-evoked activity in the ACC and mPFC when they are exposed to negative stimuli (8). They also have less robust activity in the amygdala and insula than is typical for healthy individuals exposed to positive and negative cues (6–8). Asensio and colleagues (3) demonstrated that cocaine-dependent men have a blunted neural response to positive/pleasant stimuli, but there was no difference in neural activity when exposed to negative/unpleasant emotional stimuli. Specifically, these men have lower activity than their non-drug using peers in the frontal-striatal limbic system—the orbital and mPFC, the striatum, and the thalamus. Similarly, primarily male cocaine users have demonstrated diminished activation in response to sexual stimuli in the insula and mPFC when compared to drug-naïve peers (4). These results suggest an attenuated response to naturally rewarding, positive stimuli among male cocaine users.

One study of female cocaine users demonstrated that imagery depicting cocaine use was associated with less activation in the amygdala, insula, orbito-frontal cortex, and ventral cingulate cortex than a previous study among male users (9). This suggests gender differences in response to drug-related stimuli. However, it is unclear, if these gender differences will generalize to the attenuated neural response to naturally arousing stimuli that have been observed in male cocaine users. Previous research has demonstrated that men and women have different patterns of neural activity in the pre-frontal cortex and subcortical limbic structures following exposure to emotional images (10,11). Cocaine-dependent men and women also have different patterns of medial and lateral prefrontal cortex cerebral blood flow at baseline (12) and following a dose of procaine (13). Moreover, dysfunction in the drug- and emotion-related circuitry among female users may be even more critical than that

among male users as women are more likely to have affect-related comorbidities (e.g., depression, anxiety, and post-traumatic stress disorder) (14–16). Women are also more likely to have increased rates of drug use that is precipitated by negative mood states (17,18).

Given that negative emotional stimuli and mood states appear to be a more silent factor in drug use among female versus male cocaine users, in this study we tested the hypothesis that, with a mixed gender sample of cocaine users, there would be significant differences in the neural reactivity to both positive and negative emotional images [unlike the previous study in cocaine-dependent men that observed differences in positive images only (3)]. The altered reactivity to negative images would also be consistent with prior studies in mixed gender samples of marijuana users (19,20).

Methods

Participants

The study was approved by the Institutional Review Board and all participants provided written informed consent. Forty individuals completed this study and were entered into the final data analysis: 20 non-treatment seeking cocaine-dependent individuals and 20 individuals with no lifetime history of drug or alcohol dependence (see Supplementary Material for more details in exclusion criteria). The mean age was 35.55 for drug users and 34.85 for controls, and it did not differ by user status or gender. The control group had less cigarette smokers (controls = 3, users = 17, $p < .05$), more years of education (controls = 16.15, users = 12.85; $t = 4.20$, $p < .001$), lower BDI-II scores (controls = .85, users = 5.75; $t = 3.89$, $p < .01$), and lower state anxiety (controls = 21.8, users = 28.6, $t = 3.19$, $p < .01$) than the user group. There were no significant gender differences between each group. See Table 1 for breakdown by gender and user group. Cocaine users had a mean age of first use of 20.05 ($SD = 3.50$) years old and had been using for a mean of 15.5 ($SD = 8.02$) years, and did not differ by gender.

Procedure

During the fMRI scanning session, participants were presented with blocks of highly arousing positive and negative and emotionally neutral standardized images selected from the International Affective Picture System (21). The stimuli included: 30 positive (valence $M = 6.87$, $SD = .52$), 30 negative (valence $M = 2.27$, $SD = .52$), and 30 neutral images (valence $M = 4.91$, $SD = .67$). Participants passively viewed the images and were instructed to allow themselves to feel whatever comes naturally when viewing the pictures. Because of the interest in comparing alterations in emotional response among male and female cocaine users, images were selected to be matched on arousal within each block among men and women based on standardized scores (no significant gender difference). Arousal ratings by gender and by condition were as follows: positive (men $M = 6.15$, $SD = .67$; women: $M = 5.94$, $SD = .39$); negative (men: $M = 5.97$, $SD = .60$; women: $M = 6.42$, $SD = .68$); and neutral (men: $M = 3.50$, $SD = .63$; women: $M = 3.45$, $SD = .66$). To control for potential differences in social responding among conditions (22), all images contained at least one person, and each category of images contained individuals from different racial and ethnic backgrounds.

Images were presented in two functional runs lasting 270s each. Each run consisted of nine 20s blocks: three each of positive, negative, and neutral images. Each affective block contained five images presented for 4 s each. Each image block was separated by a 10-s rest block (cross hair). Image order was pseudorandom within each block, and images were presented only once across the two runs. Following the fMRI scanning session, the participants completed a task to assess image recognition and ensure that participants did not fall asleep during image presentation. Each of the 90 previously presented stimuli, along with 90 (30 per condition) never seen stimuli, were presented randomly on a computer screen. Images were presented for an unlimited duration, until a key was pressed to indicate whether the image was previously seen during the fMRI session or not ($k = \text{yes}$; $l = \text{no}$). The number of hits (correctly identifying a seen image) and false alarms (incorrectly identifying an unseen image as seen) were counted for each stimulus type. To measure recognition, a sensitivity index ($d' = Z_{\text{hits}} - Z_{\text{false alarms}}$) was then calculated to measure the ability to distinguish between seen and never seen images (23). The effect of user status and gender on sensitivity was examined with independent samples t -tests.

Image acquisition and analysis

Scanning was performed using a 3-Tesla MRI Trio (Siemens Medical, Erlangen, Germany). High-resolution T1-weighted structural images were first acquired and used during co-registration and normalization of the functional scans [repetition time (TR) = 1750 ms, echo time (TE) = 4 ms, voxel dimensions $1.0 \times 1.0 \times 1.0$ mm, and 160 slices]. Functional scans were acquired using a standard multislice single-shot gradient echo-planar imaging sequence (TR = 2200 ms, TE = 30 ms, voxel dimensions $3.0 \times 3.0 \times 3.0$ mm, and 64×64 matrix).

Preprocessing and whole brain image analysis were conducted with SPM8 (Wellcome Department of Cognitive Neurology, London, UK), implemented in Matlab 7.14 (MathWorks, Natick, MA). Preprocessing steps are as follows: realignment to the mean image, co-registration of the T1-weighted structural scan and the mean realigned image, normalization to standard space (Montreal Neurological Institute template), and smoothing with an 8-mm Gaussian kernel. Functional images were modeled with a boxcar function convolved with the hemodynamic response function over task blocks (positive, negative, and neutral images) using the general linear model. First-level, fixed-effects contrasts were created for *positive > neutral* and *negative > neutral* for each participant. Group-level differences (user status) were calculated using second-level, random-effects analyses of the first-level contrasts for the entire sample (primary analysis), and separately for men and women (secondary analysis). The primary analysis examining the effect of user group and whether group status differentially affected response to positive and negative images was assessed with a 2 (user group) $\times$ 2 (valence) analysis of variance (ANOVA). T -tests further examined the differential response among cocaine users and controls for positive and negative images. Gender-based analyses were conducted with one-sample (within group) and two-sample (between group) t -tests. The examination of potential contributing factors was conducted by adding covariates (depression symptomatology, education, state anxiety, and cigarettes per day) to the model or directly comparing groups (marijuana dependence). All reported results met significance at $p < .05$ corrected for multiple comparisons.

(determined by Monte Carlo simulation; voxel-level threshold of $p < .005$ for at least 48 contiguous voxels; AlphaSim in REST toolbox (24)).

Results

Cocaine users relative to age- and gender-matched controls

The ANOVA revealed a main effect of user group on activation in response to emotional images. Compared to the healthy controls, the cocaine-dependent group had significantly less activation in a cluster comprised of the ACC [Brodmann areas (BA) 24, 32] and mPFC (BA 9,10), and clusters in the posterior cingulate cortex, and left temporal gyrus (BA 21). There was not a significant interaction between user group and emotional valence.

Response to pleasant/positive images—Within controls, positive images (*positive > neutral*) were associated with activation in a cluster including the bilateral ACC and mPFC (BA 9, 24, 32) that extended into the caudate and thalamus. There was also a large significant cluster containing bilateral inferior and middle occipital (BA 17, 18, 19) and temporal lobes (BA 37, 39) as well as the inferior and superior parietal lobes (BA 7, 40). Additional regions of significant activation included the posterior cingulate and precuneus, bilateral insula, and the inferior and middle frontal gyri (BA 9, 47; Figure 1, Table S1). Within users, only bilateral occipital and temporal gyri were significantly activated. Relative to controls, cocaine users had significantly less activation in a cluster containing the ACC and mPFC (BA 9, 10, 24, 32) and a cluster in the precuneus (BA 31) when viewing positive images (Figure 2). There were no regions where the users had greater activity than the controls.

Response to unpleasant/negative images—Among controls, negative images (*negative > neutral*) were associated with activity in the mPFC (BA 9,10) and a cluster containing the left lateral, middle, and inferior frontal gyri (BA 6, 9), and left posterior cingulate (BA 31). Additionally, there was a large cluster with widespread activation in bilateral inferior and middle occipital (BA 17, 18, 19) and temporal (BA 37) lobes as well as the superior parietal cortex (BA 7; Figure 3). Activation in this cluster extended into the right lateral inferior frontal cortex (BA 9) and subcortical regions including bilateral thalamus, caudate, and putamen. Among drug users, negative images were associated with activation in bilateral occipital and temporal gyri, as well as clusters in the right inferior and middle gyri (BA 47), and thalamus. Relative to controls, cocaine users had significantly less activation in the ACC and mPFC (BA 10, 24, 32) when viewing negative images (Figure 4). There were no regions where the users had greater activity than the controls.

Exploring female and male cocaine users relative to age- and gender-matched controls

Female response—Within female controls pleasant/positive images were associated with activity in the mPFC and ACC (BA 9, 10, 24, 32), as well as clusters in bilateral parietal (BA 40), temporal (BA 19, 37, 39), and occipital lobes (BA 18, 37) (Table S2). Female controls also exhibited activity in the precuneus, right lateral inferior frontal gyrus, and left thalamus. Among the female cocaine users, however, positive images evoked no significant activity relative to neutral stimuli (Figure 1). Relative to the controls, the female cocaine group had

significantly less activity in cortical limbic areas—the mPFC (BA 10) and the ACC (BA 24, 32), as well as the posterior cingulate cortex (BA 31) and angular gyrus.

Within female controls unpleasant/negative images were associated with activity in the mPFC (BA 9, 10) and two large clusters containing bilateral lateral inferior frontal and middle gyri (BA 6, 47) and insula (BA 13), extending into the caudate, putamen, and thalamus. There was also a large cluster of activation in the occipital (BA 17, 18, 19) and temporal (BA 37) lobes (Figure 3). Among the female cocaine users, negative images were associated with activity in bilateral occipital and temporal gyri (BA 17, 18, 19), as well as the right precentral gyrus (BA 6). Like with positive images, relative to the controls, female users had less activity in the ACC/mPFC (BA 10, 32), in addition to the left temporal gyrus (BA 40), fusiform gyrus, and putamen.

Male response—In non-drug using men, pleasant/positive images were associated with significant activity in a cluster containing bilateral mPFC (BA 10), ACC (BA 24, 32), insula, and caudate, as well as clusters of activity in bilateral occipital, temporal, and parietal cortices (BA 18, 19, 37, 40), and cerebellum (Figure 1; Table S3). These men also showed activation in the left insula, bilateral posterior cingulate, and right superior frontal gyrus (BA 8). As with non-drug using controls, among male users, positive images were associated with activation in bilateral occipital, temporal, and parietal cortices (BA 7, 18, 19, 37, 40). There were no activations in frontal or subcortical limbic regions, which were activated in the male controls. Direct comparisons between the control and cocaine groups of males, however, revealed no significant differences.

Among male controls, unpleasant/negative images were associated with significant activity in bilateral occipital and middle/inferior temporal lobes (BA 17, 18, 19, 37; Figure 2), as well as clusters in the right inferior frontal gyrus (BA 9) and inferior parietal (BA 40). Within male users, negative images were associated with a similar activation pattern in bilateral occipital and temporal lobes, as well as the cerebellum. As with the positive images, there were no significant differences between the male controls and drug users when viewing highly arousing negative images.

Direct gender comparison

For positive images, control men had more activation than control women in the right precuneus (xyz: 18 58 34; $k = 94$); and cocaine-dependent men had more activation than cocaine-dependent women in the right mPFC (BA 10; 9 53 13; $k = 97$) (Figure 2). Women did not have more activation than men in any regions in the control or user group for positive images. For negative images, control women had more activation than control men in clusters containing bilateral insula and postcentral gyrus (BA 6, 13; $-54 -10 22$, $k = 739$; $54 -19 52$, $k = 374$), bilateral middle cingulate ($6 -4 49$, $k = 70$), and left superior temporal gyrus (BA 22; $-39 -58 13$, $k = 330$; Figure 4). There were no regions in which men had higher brain activity than women. Cocaine-dependent men and women did not differ for negative images.

Examination of individual differences

To assess whether the group differences in education, depression symptomology, state anxiety, and cigarette smoking contributed to the main findings, correlations among these variables and response to positive and negative images were examined among the users. For the positive images, number of cigarettes smoked per day was positively associated with a cluster in the left parahippocampal gyrus/temporal lobe ($-39 -37 -8$; $k = 109$). No other significant correlations were found between education, BDI-II scores, state anxiety, number of cigarettes per day, and emotional response among the cocaine users.

Since 9 out of the 20 participants in the cocaine-dependent group were also marijuana dependent, we were able to conduct two-sample t -tests to examine whether the cocaine users who were dependent on marijuana had different functional activations from those who were not. For positive images, the marijuana-dependent cocaine users had significantly less activation in the left middle occipital cortex ($-45 -76 37$, $k = 121$) and a cluster in the right temporal lobe extending into bilateral cerebellum ($21 -31 -20$, $k = 218$) than the cocaine users who were not marijuana dependent. For negative images, there were no differences in cortical or subcortical activation between the two groups.

Recognition task results

Group comparisons revealed that users and controls did not differ in their memory of the positive, negative, or neutral images presented, as measured by d' . Additionally, there were no gender differences (all $ps > .05$).

Discussion

In this study, a standardized set of highly arousing positive and negative images was found to evoke significantly less activity in the mPFC and ACC in a mixed-gender sample of polydrug users with primary cocaine dependence relative to controls, despite equivalent memory of the pictures. When exploring group differences by gender, significant attenuation of neural responding to both positive and negative emotional stimuli was found only in female drug users, relative to their nondrug-using female counterparts. Furthermore, female users had less activation than male users for positive stimuli, and the heightened response seen among female controls relative to men for negative images was no longer demonstrated among the user group. These data highlight the importance of considering gender when investigating emotion-related processes in substance-dependent individuals.

The lack of robust activation during emotional image exposure in both cortical and subcortical limbic brain regions suggests that the cocaine-dependent polydrug users did not interpret the emotional images that are more salient or arousing than the neutral images. This is consistent with previous physiological and behavioral findings as well as neuroimaging studies of alterations in general emotional processing, including decreased arousal, of both pleasant and unpleasant affective stimuli in addiction (25–27). It is also consistent with neuroimaging studies showing that marijuana use and cigarette smoking is associated with attenuated affective response in fronto-limbic regions, including in the ACC (19,20,28).

These data suggest that an attenuated neural response to arousing nondrug stimuli may be a generalized feature of addiction that spans multiple drug classes.

Studies by Sinha et al. (29,30) have found cocaine users, and women in particular, to have a heightened corticolimbic response to a personally relevant stressful situation. Perhaps the current findings demonstrate a differential response to negative stimuli based on whether the images are perceived as salient or not, thus suggesting a dampened response to more general affective stimuli. The attenuated response to arousing stimuli in prefrontal limbic regions observed in this investigation is consistent with the impaired response inhibition and salience attribution (iRISA) model (34,35). The iRISA model proposes that drug dependence is mediated by dysfunction in the ACC and PFC, which involves a heightened response and attribution of salience to drug-related rewards at the expense of salience attributed to nondrug-related stimuli. This prefrontal dysfunction could negatively impact motivational processes that mediate drug-seeking and engagement in behaviors involving nondrug rewards or avoidance of behaviors that may result in aversive outcomes.

The inability to find pleasure in naturally rewarding stimuli (e.g., food, sex, and bonding) has been reported in cocaine-dependent individuals and may be one reason for continued drug use and relapse to cocaine after a period of abstinence in some cocaine-dependent individuals (2). Both positive and negative affective states are also related to drug-seeking and relapse (17,36,37). In non-drug using individuals, highly arousing positive and negative stimuli play a critical role in both approach and avoidance behaviors and facilitate survival and well-being (38,39). The low neural reactivity to naturally rewarding and aversive stimuli among the cocaine users may explain their devaluation of non-drug-related rewards and willingness to engage in risky behaviors that have large personal and public health and safety consequences.

Separate analyses by gender revealed that, relative to controls, female drug users had significant attenuation of emotional reactivity to both positive and negative stimuli, while male users did not. Relative to controls, the cocaine-dependent women in this study had significant dampening in the mPFC/ACC region in response to both positive and negative images. The dampened medial prefrontal response to positive images was also found among female users when compared to male users. The mPFC and ACC are involved in evaluation and interpretation of stimuli, salience detection, and motivation (40,41). There is evidence that in general women have a heightened mPFC/ACC response to emotional stimuli (42), which may be why the decrements found in the current study were more significant for cocaine-dependent women compared to controls than they were for men. The disruption in the mPFC/ACC function may be especially important for cocaine-dependent women, as these regions are implicated in normal responsivity to infant cues and could underlie the disruptions in caregiving and bonding with offspring often seen with addicted mothers (40). One explanation for this hypoactivity could be related to the high rates of trauma and/or abuse often found among substance-dependent women (41,42). An attenuated response to emotional stimuli in the ventral ACC and mPFC has been linked with trauma (46,47), and could suggest that the dampened emotional response among women developed as a coping mechanism when exposed to unpleasant stimuli. However, no participant in the current study

met the criteria for posttraumatic stress disorder. This potentially important factor should be explored in future research.

Limitations include the fact that the analyses by gender are likely not sufficiently powered to provide definitive evidence of a gender-specific attenuation to nondrug stimuli among female cocaine users (10 individuals per gender user group). The current study also included a relatively small number of individuals in the gender analyses (10 per each gender user group). Moreover, the results observed among the small number of female cocaine users may be affected by the hormonal milieu, which has been shown to potentially modulate the reinforcing effects of drugs (48). Future studies are needed to determine the effect of menstrual cycle phase, menopausal status, and contraceptive use on these gender-specific results (49). Additionally, our cocaine-dependent participants were polydrug users, almost half of whom had co-occurring marijuana dependence and most of whom were cigarette smokers. We did not find that the marijuana-dependent cocaine users had further attenuation in fronto-limbic regions, but they did have decreased reactivity for positive images. Additionally, 17 of the cocaine users were cigarette smokers (compared to 3 controls), which makes it difficult to disentangle the roles of cocaine dependence and nicotine dependence. In an effort to examine these potential contributing factors, in a covariate analysis, we found one cluster in the left parahippocampal gyrus/temporal lobe to be positively correlated with number of cigarettes smoked among the user group in this sample, though the activation did not overlap with our primary findings. Still, previous research has shown that depression severity (50) and smoking status (31,51) affect response to emotion-related stimuli, so they cannot be ruled out as affecting the attenuated responding among the cocaine users. Having arousal or valence ratings from the participants while in the scanner would have provided more insight into the emotional processing among the users, and it should be explored in a future study.

Despite the limitations to our knowledge, this is the first study to use a mixed-gender sample to examine the neural response to general emotional stimuli in cocaine-dependent polydrug using individuals. With growing momentum for unique, patient-tailored intervention strategies for cocaine users, these data present a window of opportunity for innovation. For example, while much of the emphasis in both basic and clinical addiction research focuses on eliminating the reinforcing strength of the drug and dampening craving, an alternative focus on increasing the reinforcing strength of an alternative reinforcer and amplifying the neural reactivity to these nondrug-related rewards may prove fruitful. Basic science models of addiction have explored the power of choice behavior for decades, typically employing a two-choice level pressing paradigm in one lever results in drug delivery, while the other results in delivery of an alternate reinforcer (such as food or sweetened water; 52–55). These data suggest that, as in clinical contingency management programs, drug taking can be attenuated by increasing the value of alternate positive reinforcers (56). As addiction research continues to innovate, data from this study and others like it (3) may serve as a platform for the development of treatment strategies that focus on *increasing the neural response to naturally available nondrug reinforcers*.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding

The effort for this research was supported by the National Institutes of Health (F32DA036329 to MC and K01DA0267756 to CAH).

References

1. Bechara A, Damasio H, Damasio AR. Emotion, decision making and the orbitofrontal cortex. *Cereb Cortex*. 2000; 10:295–307. DOI: 10.1093/cercor/10.3.295 [PubMed: 10731224]
2. Gawin FH. Cocaine addiction: psychology and neurophysiology. *Science*. 1991; 251:1580–1586. [PubMed: 2011738]
3. Asensio S, Romero MJ, Palau C, Sanchez A, Senabre I, Morales JL, et al. Altered neural response of the appetitive emotional system in cocaine addiction: an fMRI Study. *Addict Biol*. 2010; 15:504–516. DOI: 10.1111/j.1369-1600.2010.00230.x [PubMed: 20579005]
4. Garavan H, Pankiewicz J, Bloom A, Cho JK, Sperry L, Ross TJ, et al. Cue-induced cocaine craving: neuroanatomical specificity for drug users and drug stimuli. *Am J Psychiatry*. 2000; 157:1789–1798. DOI: 10.1176/appi.ajp.157.11.1789 [PubMed: 11058476]
5. Rutherford HJ, Williams SK, Moy S, Mayes LC, Johns JM. Disruption of maternal parenting circuitry by addictive process: rewiring of reward and stress systems. *Front Psychiatry*. 2011; 2:37.doi: 10.3389/fpsy.2011.00037 [PubMed: 21779252]
6. Phan KL, Wager T, Taylor SF, Liberzon I. Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. *Neuroimage*. 2002; 16:331–348. DOI: 10.1006/nimg.2002.1087 [PubMed: 12030820]
7. Phillips ML, Drevets WC, Rauch SL, Lane R. Neurobiology of emotion perception I: the neural basis of normal emotion perception. *Biol Psychiatry*. 2003; 54:504–514. DOI: 10.1016/S0006-3223(03)00168-9 [PubMed: 12946879]
8. Wilcox CE, Pommy JM, Adinoff B. Neural circuitry of impaired emotion regulation in substance use disorders. *Am J Psychiatry*. 2016; 173:344–361. DOI: 10.1176/appi.ajp.2015.15060710 [PubMed: 26771738]
9. 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. DOI: 10.1176/appi.ajp.161.2.233 [PubMed: 14754771]
10. George MS, Ketter TA, Parekh PI, Herscovitch P, Post RM. Gender differences in regional cerebral blood flow during transient self-induced sadness or happiness. *Biol Psychiatry*. 1996; 40:859–871. DOI: 10.1016/0006-3223(95)00572-2 [PubMed: 8896772]
11. Hofer A, Siedentopf CM, Ischebeck A, Rettenbacher MA, Verius M, Felber S, Fleischhacker WW. Gender differences in regional cerebral activity during the perception of emotion: a functional MRI study. *NeuroImage*. 2006; 32:854–862. DOI: 10.1016/j.neuroimage.2006.03.053 [PubMed: 16713306]
12. Adinoff B, Devous MD, Best SE, Chandler P, Alexander D, Payne K, Harris TS, Williams MJ. Gender differences in limbic responsiveness, by SPECT, following a pharmacologic challenge in healthy subjects. *NeuroImage*. 2003; 18:697–706. [PubMed: 12667847]
13. Adinoff B, Williams MJ, Best SE, Harris TS, Chandler P, Devous MD. Sex differences in medial and lateral orbitofrontal cortex hypoperfusion in cocaine-dependent men and women. *Gender Med*. 2006; 3:206–222.
14. Brady KT, Randall CL. Gender differences in substance use disorders. *Psychiat Clin N Am*. 1999; 22:241–252.

15. Compton WM, Cottler LB, Ben Abdallah A, Phelps DL, Spitznagel EL, Horton JC. Substance dependence and other psychiatric disorders among drug dependent subjects: race and gender correlates. *Am J Addict.* 2000; 9:113–125. DOI: 10.1080/10550490050173181 [PubMed: 10934573]
16. Sinha R, Rounsaville BJ. Sex differences in depressed substance abusers. *J Clin Psychiatry.* 2002; 63:616–627. [PubMed: 12143921]
17. Back SE, Brady KT, Jackson JL, Salstrom S, Zinzow H. Gender differences in stress reactivity among cocaine-dependent individuals. *Psychopharmacology.* 2005; 180:169–76. DOI: 10.1007/s00213-004-2129-7
18. McKay JR, Rutherford MJ, Cacciola JS, Kabasakalian-McKay R, Alterman AI. Gender differences in the relapse experiences of cocaine patients. *J Nerv Ment Dis.* 1996; 184:616–622. [PubMed: 8917159]
19. Gruber SA, Rogowska J, Yurgelun-Todd DA. Altered affective response in marijuana smokers: an fMRI study. *Drug Alcohol Depen.* 2009; 105:139–153. DOI: 10.1016/j.drugalcdep.2009.06.019
20. Rabinak CA, Sripada CS, Angstadt M, de Wit H, Phan KL. Cannabinoid modulation of subgenual anterior cingulate cortex activation during experience of negative affect. *J Neural Trans.* 2012; 119:701–707. DOI: 10.1007/s00702-011-0747-x
21. Lang PJ, Bradley MM, Cuthbert BN. International affective picture system (IAPS): affective ratings of pictures and instruction manual. Technical Report A-8. 2008
22. Britton JC, Phan KL, Taylor SF, Welsh RC, Berridge KC, Liberzon I. Neural correlates of social and nonsocial emotions: an fMRI study. *Neuroimage.* 2006; 31:397–409. DOI: 10.1016/j.neuroimage.2005.11.027 [PubMed: 16414281]
23. McNicol, D. A primer of signal detection theory. London, England: Allen & Unwin; 1972.
24. Song XW, Dong ZY, Long XY, Li SF, Zuo XN, Zhu CZ, et al. REST: a toolkit for resting-state functional magnetic resonance imaging data processing. *PLoS one.* 2011; 6:e25031.doi: 10.1371/journal.pone.0025031 [PubMed: 21949842]
25. Aguilar de Arcos F, Verdejo-García A, Peralta-Ramírez MI, Sánchez-Barrera M, Pérez-García M. Experience of emotions in substance abusers exposed to images containing neutral, positive, and negative affective stimuli. *Drug Alcohol Depen.* 2005; 78:159–167. DOI: 10.1016/j.drugalcdep.2004.10.010
26. Cheetham A, Allen NB, Yücel M, Lubman DI. The role of affective dysregulation in drug addiction. *Clin Psychol Rev.* 2010; 30:621–634. DOI: 10.1016/j.cpr.2010.04.005 [PubMed: 20546986]
27. Albein-Urios N, Verdejo-Román J, Asensio S, Soriano-Mas C, Martínez-González JM, Verdejo-García A. Reappraisal of negative emotions in cocaine dependence: dysfunctional corticolimbic activation and connectivity. *Addict Biol.* 2014; 19:415–426. DOI: 10.1111/j.1369-1600.2012.00497 [PubMed: 22978709]
28. Froeliger B, Modlin LA, Kozink RV, Wang L, Garland EL, Addicott MA, McClernon FJ. Frontoparietal attentional network activation differs between smokers and nonsmokers during affective cognition. *Psychiat Res-Neuroim.* 2013; 211:57–63. DOI: 10.1016/j.psychresns.2012.05.002
29. Li CS, 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. DOI: 10.1016/j.biopsych.2004.11.048 [PubMed: 15737663]
30. Potenza MN, Hong KIA, Lacadie CM, Fulbright RK, Tuit KL, Sinha R. Neural correlates of stress-induced and cue-induced drug craving: influences of sex and cocaine dependence. *Am J Psychiatry.* 2012; 169:406–414. DOI: 10.1176/appi.ajp.2011.11020289 [PubMed: 22294257]
31. Goldstein RZ, Volkow ND. Dysfunction of the pre-frontal cortex in addiction: neuroimaging findings and clinical implications. *Nat Rev Neurosci.* 2011; 12:652–669. DOI: 10.1038/nrn3119 [PubMed: 22011681]
32. Goldstein RZ, Volkow ND. Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. *Am J Psychiatry.* 2002; 159:1642–1652. DOI: 10.1176/appi.ajp.159.10.1642 [PubMed: 12359667]

33. Cooney NL, Litt MD, Morse PA, Bauer O, Gaupp L. Alcohol cue reactivity, negative-mood reactivity, and relapse in treated alcoholic men. *J Abnorm Psychol.* 1997; 106:243–250. DOI: 10.1037/0021-843X.106.2.243 [PubMed: 9131844]
34. Hall SM, Muñoz RF, Reus VI, Sees KL. Nicotine, negative affect, and depression. *J Consult Clin Psychol.* 1993; 61:761. doi: 10.1037/0022-006X.61.5.761 [PubMed: 7902368]
35. Keltner D, Gross JJ. Functional accounts of emotions. *Cognition & Emotion.* 1999; 13:467–480. DOI: 10.1080/026999399379140
36. Bradley MM, Lang PJ. Emotion and motivation. *Handbook of Psychophysiology.* 2000; 2:602–642.
37. Davidson RJ, Irwin W. The functional neuroanatomy of emotion and affective style. *Trends Cogn Sci.* 1999; 3:11–21. DOI: 10.1016/S1364-6613(98)01265-0 [PubMed: 10234222]
38. Volkow ND, Fowler JS, Wang GJ. The addicted human brain: insights from imaging studies. *J Clin Invest.* 2003; 111:1444–1451. DOI: 10.1172/JCI18533 [PubMed: 12750391]
39. Wager TD, Phan KL, Liberzon I, Taylor SF. Valence, gender, and lateralization of functional brain anatomy in emotion: a meta-analysis of findings from neuroimaging. *Neuroimage.* 2003; 19:513–531. DOI: 10.1016/S1053-8119(03)00078 [PubMed: 12880784]
40. Strathearn L, Mayes LC. Cocaine addiction in mothers. *Ann NY Acad Sci.* 2010; 1187:172–183. DOI: 10.1111/j.1749-6632.2009.05142.x [PubMed: 20201853]
41. Brady KT, Back SE, Coffey SF. Substance abuse and posttraumatic stress disorder. *Curr Dir Psychol Sci.* 2004; 13:206–209. DOI: 10.1111/j.0963-7214.2004.00309.x
42. Najavits LM, Gastfriend DR, Barber JP, Reif S, Muenz LR, Blaine J, et al. Cocaine dependence with and without PTSD among subjects in the National Institute on Drug Abuse Collaborative Cocaine Treatment Study. *Am J Psychiatry.* 1998; 155:214–219. [PubMed: 9464200]
43. Etkin A, Wager TD. Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. *Am J Psychiatry.* 2007; 164:1476–1488. DOI: 10.1176/appi.ajp.2007.07030504 [PubMed: 17898336]
44. Shin LM, Rauch SL, Pitman RK. Amygdala, medial prefrontal cortex, and hippocampal function in PTSD. *Ann NY Acad Sci.* 2006; 1071:67–79. DOI: 10.1196/annals.1364.007 [PubMed: 16891563]
45. Mello N. Hormones, nicotine, and cocaine: clinical studies. *Horm Behav.* 2010; 58:57–71. DOI: 10.1016/j.yhbeh.2009.10.003 [PubMed: 19835877]
46. Sakaki M, Mather M. How reward and emotional stimuli induce different reactions across the menstrual cycle. *Soc Personal Psychol Compass.* 2012; 6:1–17. DOI: 10.1111/j.1751-9004.2011.00415.x [PubMed: 22737180]
47. Lee BT, Cho SW, Khang HS, Lee BC, Choi IG, Lyoo IK, et al. The neural substrates of affective processing toward positive and negative affective pictures in patients with major depressive disorder. *Prog Neuropsychopharmacol Biol Psychiatry.* 2007; 31:1487–1492. DOI: 10.1016/j.pnpbp.2007.06.030 [PubMed: 17688985]
48. Diggs HA, Froeliger B, Carlson JM, Gilbert DG. Smoker–nonsmoker differences in neural response to smoking-related and affective stimuli: an fMRI investigation. *Psychiat Res-Neuroim.* 2013; 211:85–87. DOI: 10.1016/j.psychres.2012.06.009
49. Banks ML, Negus SS. Preclinical determinants of drug choice under concurrent schedules of drug self-administration. *Adv Pharmacol Sci.* 2012; 2012:281768. doi: 10.1155/2012/281768 [PubMed: 23243420]
50. Griffiths RR, Wurster RM, Brady JV. Discrete-trial choice procedure: effects of naloxone and methadone on choice between food and heroin. *Pharmacol Rev.* 1975; 27:357–365. [PubMed: 817307]
51. Johanson CE. Pharmacological and environmental variables affecting drug preference in rhesus monkeys. *Pharmacol Rev.* 1975; 27:343–355. [PubMed: 817306]
52. Nader MA, Woolverton WL. Effects of increasing the magnitude of an alternative reinforcer on drug choice in a discrete-trials choice procedure. *Psychopharmacology (Berl).* 1991; 105:169–174. [PubMed: 1796123]
53. Griffiths RR, Bigelow GE, Henningfield JE. Similarities in animals and human drug-taking behavior. *Advances in Substance Abuse.* 1980; 1:1–90.

Figure 1.
BOLD response to pleasant/positive images: within group effects. The control groups had widespread activation in response to positive images.

Figure 2.

BOLD response to pleasant/positive images: between group differences. Among the entire sample and among women, cocaine users had significantly less activity in the anterior cingulate cortex/medial prefrontal cortex than controls. There were no significant differences between control and drug-user men. NS = no significant activation. Cluster corrected shown, $p < .05$.

Figure 3. BOLD response to unpleasant/negative images: within group effects. The entire control group and control women had widespread occipital and limbic activation in response to negative images.

Figure 4.

BOLD response to unpleasant/negative images: between group differences. The mixed-gender sample of users and female cocaine users had significantly less activity in the anterior cingulate cortex/medial prefrontal cortex, than controls. There were no significant differences between controls and users among men. Cluster corrected shown, $p < .05$.

Table 1

Participant characteristics by group and gender.

Measure	Cocaine users (<i>n</i> = 20)		Controls (<i>n</i> = 20)	
	Male	Female	Male	Female
Age	36.60 (8.38)	34.50 (8.67)	35.20 (6.51)	34.50 (8.72)
% Caucasian ^{ac}	20 (<i>n</i> = 2)	30 (<i>n</i> = 3)	80 (<i>n</i> = 8)	60 (<i>n</i> = 6)
Education ^{ac}	12.40 (1.58)	13.30 (1.34)	17.00 (3.74)	15.30 (2.41)
Depression ^{abc}	4.50 (3.57)	7.00 (6.62)	1.10 (2.08)	.60 (1.58)
Anxiety ^{ac}	30.6 (8.88)	26.5 (8.82)	22.3 (3.47)	21.3 (3.13)
Cigarettes per day	9.50 (7.72)	7.00 (6.00)		
	<i>n</i> = 9	<i>n</i> = 8		
Age first use	18.80 (3.16)	21.30 (3.53)		
Years of use	17.80 (8.08)	13.20 (7.67)		
MJ dependence	<i>n</i> = 5	<i>n</i> = 4		

Notes. Notation indicates a significant group difference, $p < .05$.

^aUser group significantly different from control group;

^bFemale users different from female controls,

^cMale users different from male controls. There were no significant gender differences within user status group. Depression symptomology measured with Beck's Depression Inventory. State anxiety measured with the State-Trait Anxiety Inventory. Means for continuous variables reported with standard deviations in parentheses.