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Sex-Dependent Differences in the Neural Correlates of Cocaine and Emotional Cue-Reactivity in Regular Cocaine Users and Non-Drug-Using Controls: Understanding the Role of Duration and Severity of Use

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Keywords
Sex differences · Gender differences · Cocaine use disorder · Cue-reactivity · Emotional reactivity · Functional magnetic resonance imaging

Abstract
Introduction: The development of cocaine use disorder in females is suggested to be more strongly related to neural mechanisms underlying stress-reactivity, whereas in males it is suggested to be more strongly related to neural mechanisms underlying drug cue-reactivity. Existing evidence, however, is based on neuroimaging studies that either lack a control group and/or have very small sample sizes that do not allow to investigate sex differences. ***Methods:*** The main objective of the current study was to investigate sex differences in the neural correlates of cocaine and negative emotional cue-reactivity within high-risk intranasal cocaine users (CUs: 31 males and 26 females) and non-cocaine-using controls (non-CUs: 28 males and 26 females). A region of interest (ROI) analysis was applied to test for the main and interaction effects of group, sex, and stimulus type (cocaine cues vs. neutral cocaine cues and negative emotional cues vs. neutral emotional cues) on activity in the dorsal striatum, ventral striatum (VS), amygdala, and dorsal anterior cingulate cortex (dACC). ***Results:*** There were no significant sex or group differences in cocaine cue-reactivity in any of the ROIs. Results did reveal significant emotional cue-reactivity in the amygdala and VS, but these effects were not moderated by group or sex. Exploratory analyses demonstrated that emotional cue-induced activation of the dACC and VS was negatively associated with years of regular cocaine use in female CUs, while this relationship was absent in male CUs. ***Conclusions:*** While speculative, the sex-specific associations between years of regular use and emotional cue-reactivity in the dACC and VS suggest that, with longer years of use, female CUs become less sensitive to aversive stimuli, including the negative consequences of cocaine use, which could account for the observed "telescoping effect" in female CUs.

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Introduction

Cocaine is one of the most commonly used illicit substances around the world and has severe economic, psychosocial, and psychiatric consequences [1]. Generally, cocaine use disorder (CUD) is more prevalent in men than in women, but this gap is slowly closing due to increased cocaine use in women [1]. Furthermore, there are several differences between women and men in the clinical profiles of CUD with significant implications for treatment [2]. For instance, in cocaine using (CU) women, there are higher rates of comorbid psychiatric mood disorders, whereas CU men more often have comorbid alcohol abuse, attention deficit hyperactivity disorder (ADHD), and/or antisocial personality disorder [3, 4]. Accordingly, researchers have begun to explore the various mechanisms underlying differences between men and women in the development of substance use disorders (SUDs), including CUD [2]. While these differences between men and women may be related to both social cultural gender-related factors and biological sex-related factors, research often only distinguishes between men and women based on sex-assigned at birth [2]. Therefore, we will refer to sex differences, using the terms male and females, throughout the manuscript.

One of the most frequently applied methods for understanding the underlying neurobiological mechanisms in SUDs are cue-reactivity paradigms in which subjects are exposed to substance-related and/or emotional cues (e.g., pictures or videos) during functional magnetic resonance imaging (fMRI) in order to identify brain regions that mediate the development, persistence, and treatment of SUD [5]. Yet, one recent systematic review identified only six neuroimaging studies to date that statistically evaluated sex differences in these neurobiological biomarkers in SUD [6]. Ultimately, this necessitates the need for hypothesis-driven neuroimaging research into sex differences, primarily due to its implications in understanding the neurobiology of SUD [2, 5–7] and developing sex-tailored treatment designs.

Accumulating evidence demonstrates that in individuals with an SUD, substance-related cues induce hyperactivation of various regions within the salience network, including the amygdala, ventral (VS) and dorsal striatum (DS), and dorsal anterior cingulate cortex (dACC) [8, 9]. Importantly, differential reactivity of these regions to negative emotional cues has been reported in psychiatric disorders, including SUD, as well [10]. Importantly, there is increasing evidence of sex-specific involvement of the mesocorticolimbic circuit during the processing of cocaine or negative emotional cues [11–14]. More specifically, hyperactivation of the striatum, medial PFC/dACC, and amygdala in response to drug cues has been reported in male CUs, while hypoactivation of these regions is generally found in female CUs [13–16]. Similarly, hyperactivation of the mesocorticolimbic circuit in response to negative emotional cues has been demonstrated in female CUs, while hypoactivation has been demonstrated in male CUs [12, 13]. Similar findings have been demonstrated in other SUDs, like alcohol use disorder [17], although findings concerning sex differences in alcohol-cue-reactivity are conflicting [18–20]. While not all research findings are consistent [11, 15], the overall finding is that male CUs demonstrate hyperactivation of the mesocorticolimbic circuit, including the (DS) and VS, dACC, and amygdala in response to cocaine-related cues (i.e., reward), while female CUs demonstrate hyperactivation of these regions in response to negative emotional or stress-related cues [6]. Therefore, it has been suggested that substance use, including cocaine use, and relapse in females are more strongly triggered by stressors, while in males it is more strongly triggered by substance-related cues, although for the latter the evidence is not conclusive [6]. Nevertheless, results from previous studies should be taken with caution due to a lack of control groups [12, 14–16], small sample sizes (e.g., $N = 8$ to $N = 27$) [11, 12, 14, 16], and variations in studied populations ranging from non-treatment-seeking cocaine users [11, 12, 21] to individuals in treatment for a CUD [13, 15, 16]. Accordingly, the overall goal of the current study was to replicate existing findings in a large sample of non-treatment-seeking regular CUs and non-drug-using controls.

The main objective of the study was to investigate sex-dependent differences in the neural correlates of cocaine and (negative) emotional cue-reactivity within CUs (intranasal users) and non-CUs, within four regions of interest (ROIs), including the VS, DS, amygdala, and dACC. In line with previous research, it was hypothesized that male CUs, compared to female CUs and non-drug-using controls, would show stronger activation in all ROIs in response to cocaine-related cues, whereas female CUs compared to male CUs and non-drug-using controls, would show stronger activation of the ROIs to negative emotional cues [6]. A secondary objective was to explore whether there was a sex-specific relationship between cocaine use characteristics and cocaine and emotional cue-induced activation within the ROIs. Based on the assumption that cocaine use in females is more strongly driven by stress-related processes and cocaine use in males is more strongly related by reward-related processes, it was hypothesized that cocaine use characteristics

(i.e., cocaine use per month, severity of use, age of onset, and duration of regular use) would be positively related to cocaine-cue-related activation of the ROIs in male CUs, whereas these characteristics would be positively related to emotional cue-related activation of the ROIs in female CUs. Finally, several exploratory analyses were performed to investigate the effect of menstrual phase and hormonal contraceptive use on emotional and cocaine cue-reactivity, as there is increasing evidence that fluctuating sex hormones in natural cycling females and synthetic hormones in females using hormonal contraceptives strongly influence processes of positive and negative reinforcement [22, 23]. The methods and results of his exploratory analysis are described in the online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000538599).

Methods and Materials

Participants

The current study is part of a larger project aimed to investigate sex differences in the neurocognitive mechanisms underlying high-risk cocaine use [24, 25]. The total sample (n = 111), aged 18–43 years, consisted of regular CUs (n = 57, 45.6% females) and non-CUs (n = 54, 48.1% females). General exclusion criteria were potential post-traumatic stress disorder (≥2 on the Jellinek-post-traumatic stress disorder screening questionnaire) [26], an age outside the range of 18–45, and contraindications for MRI scanning. In order to include a non-CU group that did not have any SUD, including tobacco use disorder, individuals in the non-CU group were excluded if they smoked cigarettes, or had a score higher than 12 on the Alcohol Use Disorders Identification Test (AUDIT) [27], used cocaine more than five times in their life, or used illicit substances more than six times in the past 6 months. Individuals were included in the CU group when they used cocaine (intranasally) at least four times per month. Participants provided informed consent and received monetary compensation for participation. The current study was approved by the Ethics Review Board of the Faculty of Social and Behavioral Sciences, University of Amsterdam (ERB number: 2019-DP-9964).

Procedures

All participants were recruited through online and offline advertisements (e.g., social media and poster advertisements) in the area of Amsterdam, the Netherlands. Participants were asked to provide online informed consent for an online screening procedure to assess in- and exclusion criteria. On the research day, all participants provided written informed consent for participation in the study, completed all the questionnaires, and underwent an MRI scan. All participants received instructions to abstain from any drug use 24 h prior to the MRI scan (except for tobacco). No urine test was conducted to detect cocaine use because it can show traces in urine for up to 6 days after the last use in frequent users, longer than the actual effects of the substance [28]. Instead, we relied on the time-line follow-back (TLFB) method to evaluate cocaine (and other substance) use before the experiment. This method is widely acknowledged as reliable for gathering information about substance use, including cocaine, among treatment-seeking and non-treatment-seeking populations [29]. There were no other instructions regarding food or (nonalcoholic) beverage intake prior to the study procedures. The whole study procedure took approximately 90 min.

Assessment of Substance Use, Psychological Functioning, and Menstrual Phase

As non-CUs were excluded if they used substances more than 6 times in the past 6 months, substance use (except for alcohol use) was only assessed in CUs. For cocaine use severity and related problems in the past 12 months, the Drug Use Disorder Identification Test for cocaine (DUDIT) [30] was used. In addition, the TLFB procedure [29] was completed to determine cocaine use (grams and days per month), alcohol use, and cannabis use in the 28 days prior to study participation. The age of onset was measured by using an in-house questionnaire. Tobacco use was assessed using an in-house questionnaire (number of smoking days per week and cigarettes per day). Finally, a self-reported questionnaire, based on the DSM5 criteria for SUD [31], was used to apply to test for the severity of CUD, cannabis use severity, and alcohol use severity [32]. All participants completed several self-report questionnaires to assess psychological functioning. Specifically, severity of depressive symptoms was measured using the Beck Depression Inventory (BDI-II) [33], state and trait anxiety was measured by using the State and Trait Anxiety Inventory (STAI) [34], ADHD symptom severity was assessed through the ADHD Rating Scale (ADHD-RS) [35], childhood trauma through the Childhood Trauma Questionnaire (CTQ) [36] impulsivity was measured by using the Barratt Impulsiveness Scale (BIS-11) [37] and education level was assessed with an in-house questionnaire. Moreover, using an in-house developed questionnaire, hormonal contraceptive use or menstrual phase was determined. For naturally cycling females, the menstrual phase was determined using an in-house developed questionnaire that assessed the average duration of the menstrual cycle and days since last menstruation. Based on this information, females were grouped as hormonal contraceptive users, being in the luteal phase of the menstrual cycle or being in the follicular phase of the menstrual cycle for exploratory analyses. See online supplementary materials for more information.

Cocaine and Emotional Cue-Reactivity Task

During the fMRI scan, participants completed a cocaine and emotional cue-reactivity paradigm that consisted of 30 full-color cocaine images, 30 emotionally negative images, 30 neutral cocaine images, and 30 neutral emotional images, resulting in a total of 120 images (see Fig. 1). The paradigm consisted of 3 cocaine blocks, 3 emotionally negative blocks, 3 neutral cocaine blocks, and 3 neutral emotional blocks. Every block contained 10 pictures that were each presented for 2.5 s. The order of the blocks was randomized for each participant (see Fig. 1). Before the first block and after each block, two questions were shown to assess current craving (5 s) and affect (5 s) which was followed by a fixation cross that was shown another 2.5 s. The total task duration was approximately 7.5 min. All pictures were full-color images and were rescaled to a 448 × 336 pixel dimension. The negative valence pictures were selected from the 65 images of the open affective standardized image set (OASIS) [38] that were rated lowest on the

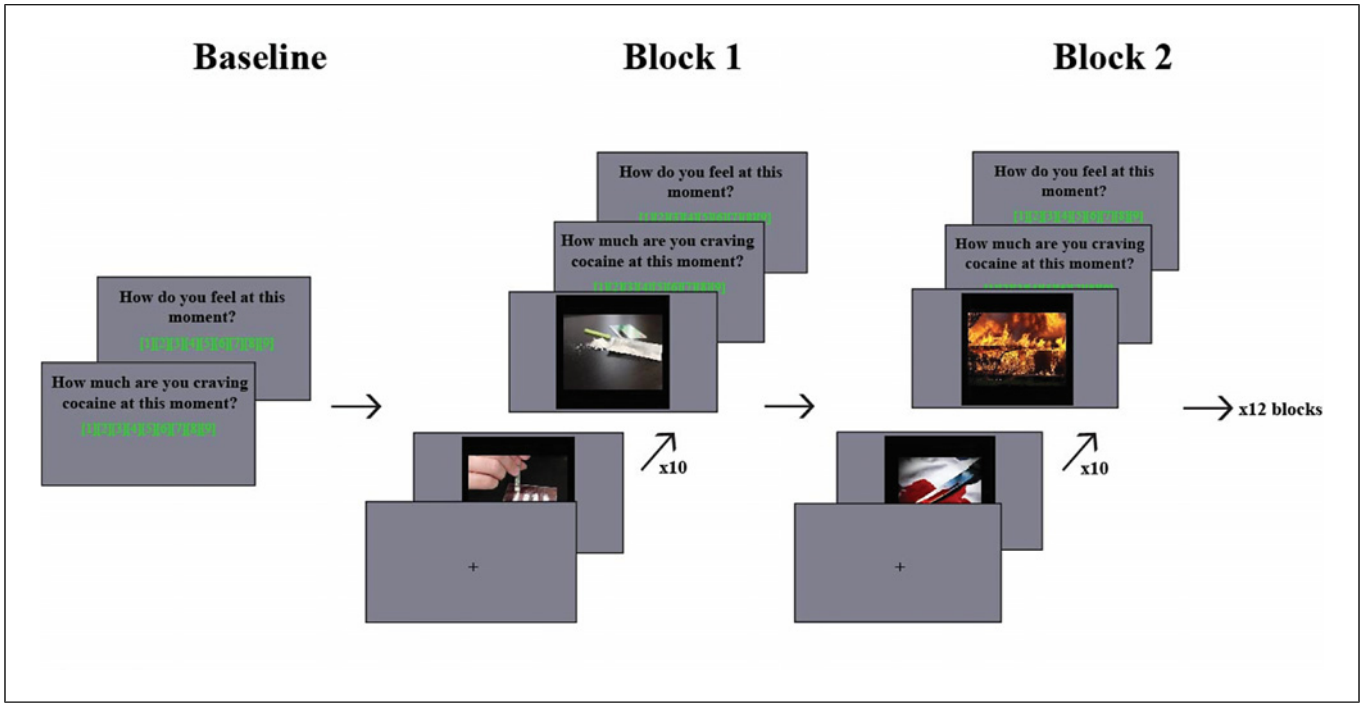

Fig. 1. The task started with a baseline measure of arousal ("How do you feel?") and craving ("How much are you craving cocaine at this moment?"). Then, a total of 12 blocks were shown in random order, which consisted of 3 emotionally negative blocks, 3 cocaine blocks, 3 control blocks matched to the emotionally negative blocks and 3 control blocks matched to the cocaine block. Each block consisted of 10 images (total 120 images) and was shown for 2.5 s. Both craving and affect were assessed after every block.

valence scale in both sexes. The neutral images were also selected from the OASIS database, particularly those that were rated neutral on the valence scale in both sexes (i.e., between 3.8 and 4.2). Cocaine pictures were derived from an earlier dataset [39]. All neutral images were matched accordingly to the negative images or cocaine images with respect to the scene presented, composition, colors, and sex of the people shown.

Participants were presented with the cue-reactivity paradigm on a screen behind the MRI scanner. They were able to view this screen through a mirror that was placed on the MRI head coil. Before the start of the fMRI task, the participants practiced answering questions using the response buttons. The questions were answered through response buttons in which participants had to select a number on a visual analog scale (VAS) that ranged from 1 ("Sad"/"Not all all") to 9 ("Happy"/"Extremely"). Participants had 5 s to respond to each question. If no response was given within 5 s, the task continued. All fMRI scans were conducted between 3:00 PM and 6:00 PM to minimize the potential effects of the time of day on craving.

fMRI Data Acquisition and Processing

All images were acquired through a 3.0-T Philips Achieva DS scanner (Philips Medical Systems, Best, the Netherlands) with a 32-channel head coil. First, a T1-3D anatomical scan (TR/TE 8.2 s/3.8; matrix 240 × 240; 1 × 1 × 1 mm^3 voxel; transverse slices) was taken. During the cue-reactivity task, echo planar images (EPIs) covering the whole brain were taken with a total of 36 ascending axial slices (3 × 3 × 3 mm^3 voxel size; slice gap 3 mm; TR/TE 2 s/28 ms; matrix 80 × 80; field of view: 216 × 216 × 130, 686 dynamics).

The MRI data were preprocessed using the fMRI prep 1.3.2 pipeline [40]. First, the anatomical data were corrected for intensity nonuniformity, skull-stripped, spatially normalized, and segmented into cerebrospinal fluid, white matter, and gray matter. Second, the functional data were corrected for susceptibility distortions by using a deformation field followed by co-registration, motion correction, and smoothing. Third, an independent component analysis for automatic removal of motion artifacts [41] was performed that automatically removed (head) motion artifacts, and the data were resampled to standard space. All scans were individually inspected after preprocessing for potential artefacts. No scans were excluded following this quality control.

The current study utilized SPM12 to further analyze the fMRI data (http://www.fil.ion.ucl.ac.uk/spm). First-level models included five separate regressors for (1) the three cocaine blocks, (2) the three neutral cocaine blocks, (3) the three negative emotional cocaine blocks, (4) the three neutral emotional blocks, and (5) the implicit baseline that contain the fixation cross (2.5 s) and the rating of craving (5 s) and affect (5 s). These regressors were modelled with a box-car function with the duration of the blocks and convolved with a canonical hemodynamic response function. A high pass filter (1/128 Hz) was included in the first-level model to correct for low-frequency signal drift. The following four first-level contrasts were subsequently entered into a second-level

whole-brain model: one contrast for the main effect of cocaine blocks, one contrast for the main effect of the neutral cocaine blocks, one contrast for main effect of the negative emotional blocks, one contrast for the main effect of neutral emotional blocks. Subsequently, the Marsbar toolbox (http://marsbar.sourceforge.net) was used to extract the mean activity (beta-weights) for the contrasts for each ROI (left and right DS, VS, amygdala, and dACC). The automated anatomical labeling (AAL) atlas [42] was used to define the amygdala. In line with previous research, the dACC was defined as the higher (z-coordinate> 7) part of the ACC defined by the AAL atlas, and the VS was defined as the nucleus accumbens from the Harvard-Oxford subcortical structure probability atlas (http://www.cma.mgh.harvard.edu/fsl_atlas.html) [18]. The DS was subsequently defined as the caudate and putamen from the AAL atlas [42] minus the VS. An average of the left and right values for each ROI was calculated and subsequently used as the dependent variable in the ROI analyses.

Statistical Analyses

Potential sex and group differences in demographic and clinical characteristics were analyzed using a one-way ANOVA, including as ADHD symptoms, depression, anxiety, childhood trauma, and impulsivity. In case of sex differences, group differences, or sex-specific group differences in these variables, these variables were included as confounders in follow-up exploratory analyses to determine whether sex and/or group differences in cocaine cue or emotional reactivity might (in part) be explained by group and/or sex differences in these demographic and clinical characteristics. For the CU group, sex differences in DSM5 symptom count for cocaine, alcohol, and cannabis use disorder were tested using χ^2 tests. Sex differences in age of onset of regular cocaine use, years of regular cocaine use, cocaine use per month, cocaine use severity (DUDIT scores), and nicotine use severity (FTND-scores) were analyzed using a one-way ANOVA. To analyze group and sex differences in cue-induced craving and affect, difference scores in craving and affect for each block were calculated by subtracting the scores after the block from the scores before the block. The means of these difference scores for each block type were subsequently used as outcome variables in two mixed factorial ANOVAs, with cue type (cocaine, neutral image, negative emotional, neutral emotional) as within subject factor, group and sex as between subject factor, and difference scores for craving and negative affect as outcome variables. With regard to the assessment of affect during the cue-reactivity paradigm, the current study asked for the participant's rating in affect (a negative value represented a negative affect and a positive value reflected a positive affect). Negative or lower scores represent an increase in negative affect, while increases or positive scores represent an increase in positive affect. A one-way ANOVA was performed to test for sex and/or group differences in percentages of questions answered within the allotted timeframe (5 s) during the fMRI task. Lastly, a one-way ANOVA was used to test for group and/or sex differences in framewise displacement (FD).

Sex-dependent differences in negative emotional and cocaine cue activation of the ROIs were tested using mixed factorial ANOVAs. More specifically, cue type (cocaine and neutral or negative emotional and neutral emotional) was included as within subject factor in two separate analyses with group and sex as independent variables and mean activation of the voxels within each ROI as dependent variable. Mean FD, as quantified by the algorithm in the fMRI prep pipeline [43] was entered as a covariate of non-interest in all analyses. In case of significant sex by group by cue type interaction effects, within-group and sex follow-up tests were performed.

To investigate the moderating role of cocaine use characteristics on emotional and cocaine cue-reactivity, several within CU group mixed factorial ANOVA analyses were performed, with cue type (cocaine and neutral cocaine or negative emotional and neutral emotional) as within subject factor in two separate analyses, mean activation in the ROIs as the dependent variable, sex as between-group factor, and FD as covariate of non-interest. The following variables were included as covariates of interest, including years of regular cocaine use (current age minus onset age of regular use), age of onset of regular cocaine use, cocaine use severity (DUDIT scores), and cocaine use per month in grams. In case of significant sex by covariate interaction effects, within-sex follow-up tests were performed.

An exploratory analysis was performed to investigate differences between cocaine cue- and emotional cue-reactivity and whether group and/or sex effects are present. To this extent, an additional RM ANOVA was performed with cocaine cue-reactivity (cocaine cues – neutral cocaine cues) and emotional cue-reactivity (negative emotional cues – neutral cues) as within subject factor, and group as between subject factor, mean activation in the ROIs as dependent variable and FD as covariate of non-interest.

To test for main and interaction effects of group, sex, and cue type outside the predefined ROIs, the first-level contrasts (one contrast for the cocaine blocks, one contrast for the neutral cocaine blocks, one contrast for the negative emotional blocks, one contrast for the neutral emotional blocks) were entered into a second-level full-factorial whole-brain model. Here, we tested for the main effect of block type (cocaine block – neutral cocaine block, and negative emotional block – negative neutral block), as well as group, sex, and group by sex differences in these effects. An exploratory analysis was performed to test for group and/or sex differences between cocaine cue (cocaine cue-neutral cocaine cues) and emotional cue (emotional cues – neutral emotional cues) reactivity. In these analyses, mean FD values for each subject were included as covariate of non-interest to account for potential motion differences. Whole-brain analyses were family-wise error (FWE) rate corrected on cluster level ($p < 0.05$), with an initial height threshold on voxel level of $p < 0.001$.

For all analyses, only the statistics for the significant results will be reported. Because we include four ROIs in our ROI analyses, we applied a Bonferroni correction to all ROI results. As such, only p values below 0.0125 are considered significant. Findings with p values between 0.0125 and 0.05, and their corresponding effect sizes will be reported as trend significant as this can provides important insight for follow-up research. The methods for analyzing the influence of menstrual phase and hormonal contraceptive use are described in the online supplementary material.

Results

Demographics, Clinical Characteristics, and Task Performance

Four values of age of onset were missing, due to a technical failure of the data collection software. As excluding these participants from all analyses was deemed

undesirable, linear regression imputation was used to replace these missing values, based on the regression between age and onset age of regular use in males and females, separately. The following formula was used for years of regular use: B (constant) + B (age) × age. This resulted in the following formulas: 4.11 + (0.69 × age) for males and 10.5 + (0.41 × age) for females.

The CU and non-CU groups did not differ in age. Yet, the CU group reported significantly higher scores on ADHD symptom severity, depressive symptoms, impulsivity, childhood trauma, and drinking severity. Moreover, there was a sex-by-group interaction effect in childhood trauma, depressive symptoms, and impulsivity, where female CUs reported significantly higher scores. Within the non-CU group, there were no sex differences in these variables. Accordingly, these clinical characteristics have been included as potential confounders in exploratory analyses of the cocaine and emotional cue-reactivity data. Of all participants, 1 non-CU female, 5 non-CU males, 6 CU females, and 6 CU males had a score above 40 on the state anxiety questionnaire, which is indicative of a clinical level of anxiety [44]. Moreover, 2 non-CU females, 1 non-CU males, 15 CU females, and 7 CU males had a score of 14 or higher on the BDI-II questionnaire, which is indicative of a clinical level of depression [33]. None of the non-CUs reported the use of GHB, cocaine, amphetamine, or methamphetamine, but some reported the use of cannabis, ketamine, N20 gas, LSD, and XTC/MDMA. An overview of all demographic and clinical data and statistics is presented in Table 1.

Male and female CUs were well matched on cocaine use severity, cocaine use per month, and years of regular use. However, females reported regular use of cocaine at an earlier age than males. 77.4% of the male CUs and 88.5% of the female CUs met the DSM5 criteria for a mild, moderate, or severe CUD. Of all male CUs, 77.4% met the DSM5 criteria for a mild, moderate, or severe AUD, 29% met the DSM5 criteria for a cannabis use disorder. 51.1% of all male CUs used tobacco. Of all female CUs, 76.9% met the DSM5 criteria for an AUD, and 15.4% met the DSM5 criteria for a cannabis use disorder. 73.1% of all female CUs used tobacco. An overview of all substance use characteristics and statistics is presented in Table 2.

During the fMRI task, affect and craving were both assessed 12 times. The number of questions answered during the fMRI scan ranged from 20 (98.4%) to 24 (100%): non-CU females responded to 100% of the questions, non-CU males responded to 99.4% of all questions, CU females responded to 99.0% of all questions, and CU males responded to 98.5% of all questions. There were no group, sex, or group-by-sex interactions in task performance. FD during the fMRI task was significantly higher in CUs (0.18 ± 0.10 SD) than in non-CUs (0.12 ± 0.10 SD), but FD was not different between males or females.

Cocaine Cue-Reactivity

Subjective Effects

Cocaine cue-induced craving was significantly moderated by group ($p < 0.001$, $\eta^2 = 0.24$) but not by sex. More specifically, cocaine cues significantly increased craving in CUs ($p < 0.001$, $\eta^2 = 0.46$) but not in non-CUs (see Fig. 2a). There were no significant main or interaction effects between group, sex, and cue type on cocaine-cue-induced affect.

Group and Sex Differences in Cocaine Cue-Reactivity

Cocaine cues did not induce any significant activation in any of the ROIs (i.e., DS, VS, amygdala, and dACC), nor was this moderated by group or sex (see Fig. 2b). These effects did not change upon correcting for potential confounders (i.e., ADHD, BDI, BIS, CTQ, and AUDIT for the group effects; BIS for the sex effects and BIS, BDI, and CTQ for the group-by-sex interaction effects).

Within CU Group Analyses on the Relationship Cocaine Use Characteristics and Cocaine Cue-Reactivity in the ROIs

Within the CU group, cocaine cue-reactivity was unrelated to years of regular use, onset age of regular use, cocaine use per month in grams, and cocaine use severity. However, the relationship between cocaine use severity (DUDIT score) and cocaine cue-reactivity in the DS ($p = 0.029$, $\eta^2 = 0.10$) and amygdala ($p = 0.024$, $\eta^2 = 0.11$) was trend-significantly moderated by sex. To interpret this interaction, follow-up regression analyses were applied within males and females separately. While the association between cocaine use severity and cocaine cue-reactivity in the DS and amygdala were not significant within sexes separately, they did indicate a positive relationship between cocaine use severity and cue-reactivity in the DS for female CUs, while this relationship was absent in male CUs (see Fig. 2c). Similarly, cocaine use severity was positively related to cocaine cue-reactivity in the amygdala in female CUs, while this relationship was negative in male CUs (see Fig. 2d).

Table 1. Demographic and clinical information in male (non-)cocaine users and female (non-)cocaine users

	Cocaine users		Controls		Main effect group	Main effect sex	Sex * group interaction
	Males (n = 31)	Females (n = 26)	Males (n = 28)	Females (n = 26)			
Age	29.2 (6.8)	26.5 (6.9)	25.9 (5.7)	26.1 (5.1)	p = 0.12, η^2 = 0.02	p = 0.28, η^2 = 0.01	p = 0.23, η^2 = 0.01
Education[a], n (%)					p = 0.09, x^2 = 21.6	p = 0.34, x^2 = 15.6	
Elementary school	0 (0%)	1 (3.7%)	0 (0%)	0 (0%)			
(Prevocational) secondary	0 (0%)	0 (0%)	2 (7.1%)	0 (0%)			
Senior general/ preuniversity	15 (48.4%)	13 (48.1%)	11 (39.3%)	10 (35.7%)			
Higher professional/ university	16 (51.6%)	13 (48.1%)	15 (53.6%)	18 (64.3%)			
State anxiety (STAI)	23.8 (8.4)	34.0 (7.5)	31.5 (8.0)	30.6 (6.4)	p = 0.12, η^2 0.02	p = 0.91, η^2 < 0.01	p = 0.09, η^2 = 0.03
ADHD symptom severity (ADHD-RS)	48.0 (22.7)	50.2 (28.0)	35.8 (21.8)	27.7 (19.0)	p < 0.01, η^2 = 0.13	p = 0.50, η^2 < 0.01	p = 0.24, η^2 = 0.01
Depression (BDI-II)	9.0 (8.6)	14.6 (8.2)	5.0 (4.7)	4.5 (5.2)	p < 0.01, η^2 = 0.22	p = 0.07, η^2 = 0.03	p < 0.05, η^2 = 0.06
Impulsivity (BIS-11)	63.8 (10.6)	71.9 (12.6)	55.9 (8.3)	55.6 (8.9)	p < 0.01, η^2 = 0.27	p < 0.05, η^2 = 0.04	p < 0.05, η^2 = 0.04
Childhood trauma (CTQ)	48.1 (8.3)	55.0 (15.7)	46.3 (5.7)	45.0 (4.3)	p < 0.01, η^2 = 0.09	p = 0.12, η^2 = 0.02	p < 0.05, η^2 = 0.05
Menstrual phase/hormonal contraceptive use[b], n (%)							
Follicular phase		3 (11.5%)		6 (23.1%)			
Luteal phase		5 (19.2%)		7 (26.9%)			
Hormonal contraceptive user		16 (61.5%)		13 (61.5%)			
Alcohol use severity (AUDIT)	10.7 (5.8)	12.3 (3.9)	3.8 (3.2)	4.4 (3.1)	*p = <0.01,* η^2 = 0.45	p = 0.15, η^2 = 0.02	*p = 0.49,* η^2 < 0.01
Substance use in past 6 months (yes)							
GHB	n = 8	n = 11	n = 0	n = 0			
Amphetamine	n = 12	n = 14	n = 0	n = 0			
Methamphetamine	n = 2	n = 4	n = 0	n = 0			
Cannabis	n = 23	n = 20	n = 4	n = 1			
Ketamine	n = 22	n = 17	n = 1	n = 0			
N2O gas	n = 19	n = 18	n = 2	n = 2			
LSD	n = 6	n = 6	n = 1	n = 0			
XTC/MDMA	n = 23	n = 23	n = 0	n = 4			

STAI, State-Trait Anxiety Inventory; ADHD-RS, Attention Deficit Hyperactivity Disorder-Rating Scale; BDI, Beck Depression Inventory II; BIS, Barratt Impulsiveness Scale; CTQ, Childhood Trauma Questionnaire; AUDIT, Alcohol Use Disorders Identification Test. [a]Highest finished educational level. [b]See online supplementary material for methods.

Table 2. Substance use characteristics in male and female cocaine users

	Cocaine users		Main effect sex
	Male (n = 31)	Female (n = 26)	
CUD (DSM5)[a]			p = 0.49, φ = 0.04
No CUD	7 (22.6%)	3 (11.5%)	
Mild CUD	7 (22.6%)	4 (15.4%)	
Moderate CUD	6 (19.4%)	7 (26.9%)	
Severe CUD	11 (35.5%)	13 (50.0%)	
Age of onset regular cocaine use	24.2 (5.3)	21.3 (4.4)	**p < 0.05, η^2 = 0.08**
Years of regular cocaine use	4.7 (4.4)	5.2 (5.3)	p = 0.69, η^2 < 0.01
Cocaine use per month, g	5.9 (4.9)	3.9 (3.8)	p = 0.10, η^2 = 0.05
Cocaine use severity (DUDIT)	16.9 (5.9)	16.4 (4.7)	p = 0.74, η^2 < 0.01
Range	8–29	10–28	
Alcohol use disorder (DSM5)[a]			p = 0.71, φ = 0.02
No alcohol use disorder	7 (22.6%)	6 (23.1%)	
Mild alcohol use disorder	7 (22.6%)	3 (11.5%)	
Moderate alcohol use disorder	7 (22.6%)	6 (23.1%)	
Severe alcohol use disorder	10 (32.2%)	11 (42.3%)	
Cannabis use disorder (DSM5)[a]			p = 0.32, φ = 0.06
No cannabis use disorder	22 (71.0%)	22 (84.6%)	
Mild cannabis use disorder	4 (12.9%)	1 (3.8%)	
Moderate cannabis use disorder	4 (12.9%)	1 (3.8%)	
Severe cannabis use disorder	1 (3.2%)	2 (7.7%)	
Tobacco user	21 (51.1%)	23 (73.1%)	p = 0.34, φ = 0.01
Nicotine Use Severity (FTND)[b]	2.30 (2.49)	2.81 (2.38)	p = 0.50, η^2 = 0.01
Low dependence	13 (61.9%)	11 (47.8%)	
Mild to moderate dependence	3 (14.3%)	6 (26.1%)	
Moderate dependence	7 (33.3%)	2 (8.7%)	
High Dependence	0 (0%)	4 (17.4%)	

DSM5, Fifth edition of the Diagnostic and Statistical Manual of Mental Disorders Diagnostic; DUDIT, Drug Use Disorder Identification Test for cocaine; AUDIT, Alcohol Use Disorders Identification Test. [a]2–3 symptoms are mild CUD, 4–5 symptoms are moderate CUD, and six or more symptoms are severe CUD. [b]FTND = Fagerström test of nicotine dependence; mean scores are reported only for participants that indicated that they smoke. 1–2 = low dependence, 3–4 = low to moderate dependence, 5–7 = moderate dependence, 8+ = high dependence.

Emotional Cue-Reactivity

Subjective Effects

On average participants reported significantly more negative affect (and thus less positive affect) (p < 0.001, η^2 = 0.57) and lower craving scores (p < 0.001, η^2 = 0.10) following the presentation of negative emotional cues compared to neutral cues (see Fig. 3a). Furthermore, emotional cue-induced craving was significantly moderated by group (p < 0.01, η^2 = 0.10). More specifically, results demonstrated that emotional cues significantly reduced craving in CUs (p < 0.01, η^2 = 0.19), but not in non-CUs. The other main and interaction effects were not significant.

Group and Sex Differences in Emotional Cue-Reactivity

Mixed factorial ANOVAs investigating neural activation within the ROIs, with CU group and sex as independent factors and FD as covariate of non-interest, demonstrated that emotional cues significantly increased neural activation in the DS (p = 0.01, η^2 = 0.06) and amygdala (p < 0.001, η^2 = 0.22) (see Fig. 3b). Moreover, emotional cue-induced activation of the amygdala was trend-significantly stronger in females compared to males (p = 0.046, η^2 = 0.04). Emotional cue-induced neural activation of the ROIs did not differ between CUs and non-CUs. These effects did not change upon correcting for

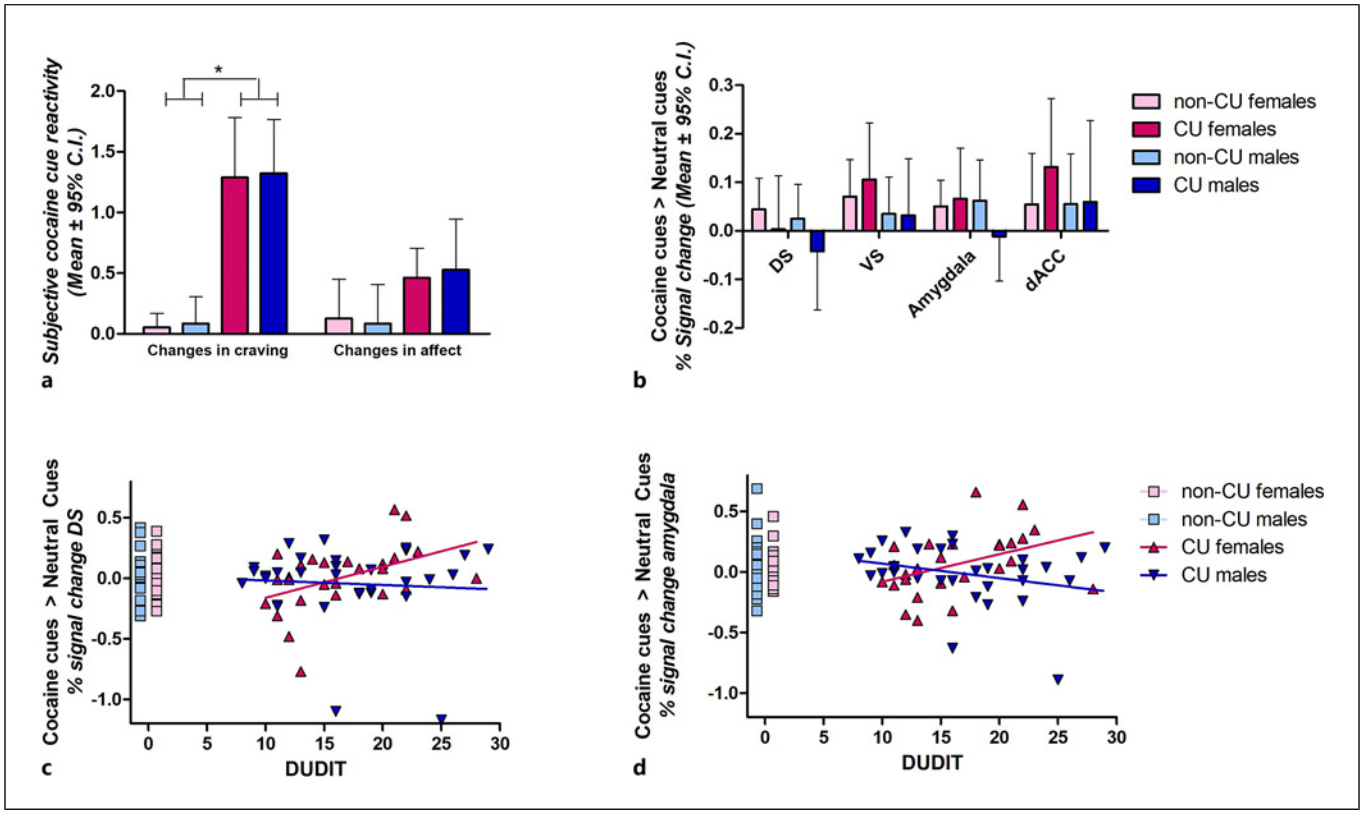

Fig. 2. a The values represent the scores for craving and affect following the cocaine cues deducted from the scores for craving and affect following the neutral cocaine blocks. Thus, negative values reflect an increase in negative affect or a decrease in positive affect. Self-reported craving significantly increased following cocaine cues versus neutral cues in CUs ($p < 0.001$) but not in non-CUs ($p = 0.23$). There were no group or sex effects on cocaine cue-induced negative affect. There was a significant interaction effect between cocaine use severity (DUDIT) scores and cocaine cue-reactivity in the DS ($p = 0.029$) and amygdala ($p = 0.024$). **b** There were no main effects of cocaine cues versus neutral cues on activation in the ROIs. **c** Cocaine cue-induced activation of the DS was positive but nonsignificantly associated with cocaine use severity in female CUs ($B = 0.33$, $p = 0.09$), while this relationship was negative and nonsignificant in male CUs ($B = -0.07$, $p = 0.73$). **d** Cocaine cue-induced activation of the amygdala was positive but nonsignificantly associated with cocaine use severity in female CUs ($B = 0.31$, $p = 0.12$), while this relationship was negative and nonsignificantly in male CUs ($B = -0.27$, $p = 0.15$).

potential confounders (i.e., ADHD, BDI, BIS, CTQ, and AUDIT for the group effects; BIS for the sex effects and BIS, BDI, and CTQ for the group-by-sex interaction effects).

Within CU Group Analyses on the Relationship between Cocaine Use Characteristics and Emotional Cue-Reactivity in the ROIs

The relationship between years of regular use and emotional cue-reactivity in the VS ($p = 0.013$, $\eta^2 = 0.13$) and dACC ($p < 0.01$, $\eta^2 = 0.16$) was significantly moderated by sex. Follow-up regression analyses demonstrated a significant negative association between years of regular cocaine use and emotional cue-induced activation of the dACC in female CUs ($B = -0.47$, $p = 0.02$), while there was a nonsignificant relationship in male CUs (see Fig. 3c). Similarly, emotional cue-reactivity in the VS was significantly and negatively related to years of regular use in female CUs ($B = -0.54$, $p = 0.002$), while this relationship was nonsignificant in male CUs (see Fig. 3d).

Exploratory Whole-Brain Analyses

Whole-brain analyses were family-wise error (FWE) rate corrected on cluster level ($p < 0.05$), with an initial height threshold at voxel level of $p < 0.001$.

Cocaine Cue-Reactivity

Cocaine cues induced significant activation in the reward network, including the bilateral medial PFC, dACC, right caudate, left amygdala, and putamen (Table 3).

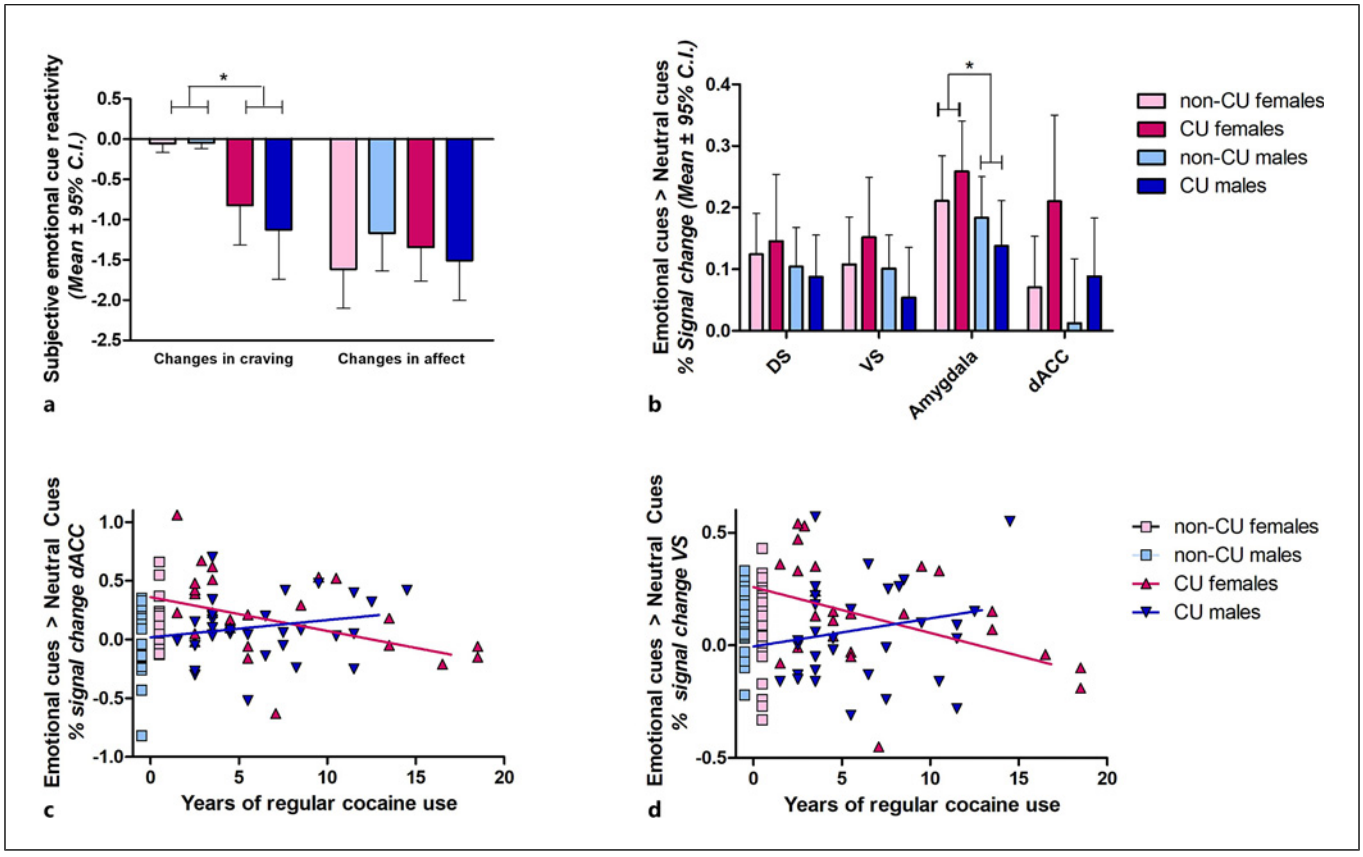

Fig. 3. a The values represent the scores for craving and affect reported following the negative emotional block deducted from the scores for craving or affect reported following the neutral emotional block. Thus, negative values reflect an increase in negative affect or a decrease in positive affect. Emotional cues significantly reduced craving in CUs ($p < 0.01$), but not in non-CUs. Emotional cues significantly reduced affect in both groups ($p < 0.001$). **b** There was a significant effect of emotional versus neutral cues in the DS ($p = 0.01$) and amygdala ($p < 0.001$). The relationship between years of regular cocaine use and emotional cue-reactivity in the dACC ($p < 0.01$) and VS ($p = 0.013$) was significantly moderated by sex. **c** Emotional cue-induced activation of the dACC was negatively associated with years of regular use in females ($B = -0.47$, $p = 0.02$), but this relationship was positive and non significant in males ($B = 0.38$, $p = 0.08$). **d**. Emotional cue-induced activation of the VS was negatively associated with years of regular use in female CUs ($B = -0.54$, $p = 0.002$) while this relationship was positive and nonsignificant in male CUs ($B = 0.28$, $p = 0.20$).

These effects were, however, not moderated by sex and or group, indicating that these patterns of activity were not specific for the CU group. For visualization purposes, the within-group task-effects are shown in online supplementary Figure 3.

Emotional Cue-Reactivity

Emotional cues significantly increased activation of various regions in the mesocorticolimbic circuit, including the medial prefrontal cortex, temporal cortex, and visual cortex (Table 4; Fig. 4a). There was a significant group by stimulus type interaction effect in the right insula. More specifically, the right insula was more strongly activated by emotional cues in CUs compared to non-CUs (see Fig. 4fig4b). There was also a significant stimulus type by sex interaction effect, demonstrating that the right insula and amygdala were more strongly activated in females compared to males. However, there were no significant sex-dependent differences in the neural correlates of emotional cue-reactivity between CUs and non-CUs. For visualization purposes, the within-group task-effects are shown in online supplementary Figure 4.

The Relationship between Cocaine Cue- and Emotional Cue-Reactivity

The ROI analyses demonstrated that the DS (F1, 106 = 2.29, $p = 0.05$, $\eta^2 = 0.04$) and amygdala (F1, 106 = 8.15, $p < 0.01$, $\eta^2 = 0.07$) responded significantly stronger

Table 3. Main and interaction effects of stimulus type (cocaine vs. neutral), sex, and group

Cluster pFWE corrected	Cluster size	Peak voxel Z-value	MNI coordinates	Region
Cocaine cue reactivity				
Main effect stimulus type				
Cocaine cues > neutral cues				
<0.001	1,920	7.09	0, 64, 0	Frontal_Sup_Medial_L
		3.93	12, 68, 6	Frontal_Sup_Medial_R
		5.91	−2, 46, −2	Cingulum_Ant_L
		3.72	4, 38, 10	Cingulum_Ant_R
		5.85	−10, 66, −4	Frontal_Med_Orb_L
		3.76	−20, 68, 14	Frontal_Sup_L
		3.4	16, 52, 12	Frontal_Sup_R
<0.001	1,041	6.8	−12, −98, −2	Calcarine_L
		5.39	18, −96, 4	Calcarine_R
<0.001	1,365	6.54	−2, −50, 30	Cingulum_Post_L
		6.03	10, −52, 26	Precuneus_R
		3.75	−6, −46, 10	Precuneus_L
0.007	252	5.99	64, −14, 28	Postcentral_R
<0.001	928	5.93	−62, −22, 36	SupraMarginal_L
		5.12	−54, −28, 40	Parietal_Inf_L
0.001	344	4.5	6, 12, −4	Caudate_R
		3.48	−14, −4, −18	ParaHippocampal_L
		3.43	−18, −4, −16	Amygdala_L
		3.37	−12, 10, −8	Putamen_L
<0.001	602	5.26	56, 26, 26	Frontal_Inf_Tri_R
		3.26	48, 38, 34	Frontal_Mid_R
0.009	241	5.05	−14, −80, −32	Cerebelum_Crus2_L
Neutral cues > Cocaine cues: no significant clusters				
Stimulus type * group interaction effect: no significant clusters				
Stimulus type * sex interaction effect: no significant clusters				
Stimulus type * sex * group interaction effect: no significant clusters				

MNI, Montreal Neurological Institute; FWE, family-wise error.

to negative emotional cues (vs. emotional neutral cues) than to cocaine cues (vs. neutral cocaine cues), but the effects in the DS did not remain significant following a Bonferroni correction. This effect did not differ between groups and/or sexes. Similar effects were found for the whole-brain analyses, that demonstrated that negative emotional cues (vs. neutral emotional cues) elicited stronger activation compared to cocaine cues (vs. neutral cues) within the bilateral medial superior and inferior frontal gyrus as well as within the cerebellum and right middle temporal gyrus (Table 5). Negative emotional cues (vs. neutral emotional cues) elicited less activation compared to cocaine cues (vs. neutral cues) within the bilateral posterior cingulate cortex and precuneus (Table 5).

Exploratory Analyses on the Influence of Menstrual Cycle and Hormonal Contraceptive Use on Cocaine and Emotional Cue-Reactivity

Exploratory analyses on the influence of menstrual cycle phase and hormonal contraceptive use did not reveal any significant effects on cocaine cue-reactivity in any of the ROIs (online suppl. Table 1; online suppl. Fig. 1). However, emotional cue-induced activation of the DS was significantly stronger in females in the luteal phase of their menstrual cycle, compared to males. On the other hand, emotional cue-induced activation of the amygdala was significantly stronger in females using hormonal contraceptives compared to males (online suppl. Table 2; online suppl. Fig. 2). It should be noted that these exploratory subgroup analyses were performed on very small sample sizes as there were 13 non-CU females and

Table 4. Main and interaction effects of stimulus type (emotional vs. neutral), sex, and group

	Cluster *p* value FWE-corrected	Cluster size (in voxels)	Peak voxel z-value	Peak voxel MNI coordinates (x, *y*, z)	Region
Emotional cue reactivity					
Main effect stimulus type					
Emotional cues > neutral cues					
	<0.001	59,230	>9.99	50, −72, 12	Temporal_Mid_R
			>9.99	44, −48, −16	Fusiform_R
			>9.99	−38, −58, −16	Fusiform_L
			>9.99	48, −70, −8	Temporal_Inf_R
			>9.99	−46, 48, −20	Temporal_Inf_L
			>9.99	42, −82, 10	Occipital_Mid_R
			>9.99	20, −4, −14	Hippocampus_R
			>9.99	−8, −78, −42	Cerebelum_7b_L
	<0.001	5,589	7.09	−4, 60, 28	Frontal_Sup_Medial_L
			6.06	8, 64, 26	Frontal_Sup_Medial_R
			5.78	2, −6, 38	Cingulum_Mid_L
			5.77	8, 8, 60	Supp_Motor_Area_R
			5.28	4, 20, 26	Cingulum_Ant_R
			4.9	0, 56, −8	Frontal_Med_Orb_L
	<0.001	2382	6.72	−32, −6, 50	Precentral_L
			6.64	−40, 8, 28	Frontal_Inf_Oper_L
			5.02	−42, −14, 44	Postcentral_L
			4.06	−20, 6, 56	Frontal_Mid_L
	<0.001	454	4.79	6, −46, 52	Precuneus_R
			4.65	−4, −48, 50	Precuneus_L
	0.029	184	4.72	−54, −10, −12	Temporal_Mid_L
Neutral cues > emotional cues					
	0.035	175	4.37	44, −50, 42	Parietal_Inf_R
			3.65	46, −58, 40	Angular_R
Stimulus type (emotional cues > neutral cues) * group interaction effect					
CU > non-CU	0.017	210	4.15	38, 12, −14	Insula_R
Non-CU > CU	No significant clusters				
Stimulus type (emotional cues > neutral cues) * sex interaction effects					
Female > male	0.043	166	4.12	−36, 0, −12	Insula_L
			3.81	−28, −6, −12	Amygdala_L
Stimulus type * sex * group interaction effects: no significant clusters					

MNI, Montreal Neurological Institute; FWE, family-wise error.

16 CU females on hormonal contraceptives, 6 non-CU females and 3 CU females in the follicular phase of the menstrual cycle, and 7 non-CU females and 5 CU females in the luteal phase of the menstrual cycle.

Discussion

In the past decade, increases in cocaine use in females have been observed in comparison to males [1]. There are indications for sex differences in clinical profiles of persons with CUD, such as psychiatric comorbidity and an accelerated progression to compulsive use in female CUs [2]. Yet, the exact neural mechanisms underlying sex differences underlying the development of CUD remain poorly understood with potential implications for the development of sex-tailored treatment strategies [7]. Accordingly, the main objective of the current study was to investigate sex differences in the neural correlates of cocaine and negative emotional cue-reactivity within regular intranasal cocaine users and non-cocaine-using controls in various ROIs, including the DS, VS, amygdala, and dACC.

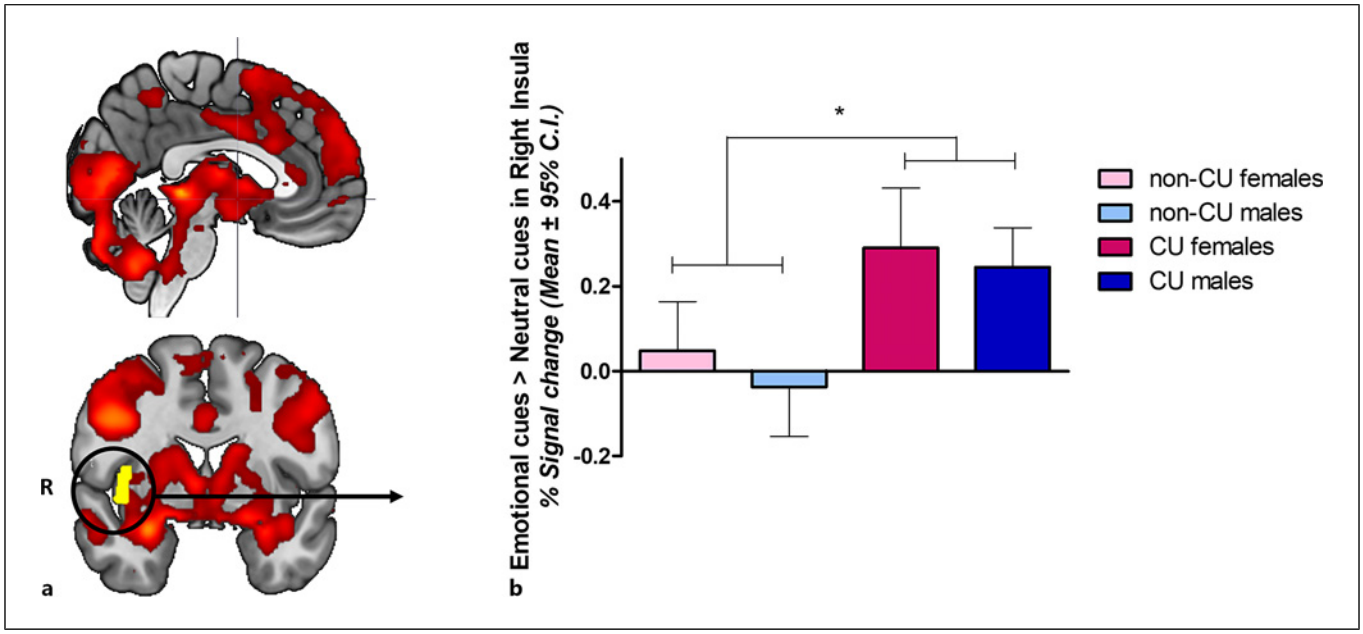

Fig. 4. a Emotional cues significantly increased activation of the salience network. The threshold of the figure is $p < 0.001$, uncorrected. **b** There was a significant group by stimulus type interaction effect in the left insula. The threshold of the figure is $p < 0.001$, uncorrected. NB: left is right; figure made in MRIcron.

Table 5. Association between emotional cue- and cocaine cue-reactivity

Cluster *p* value FWE-corrected	Cluster size (in voxels)	Peak voxel z-value	Peak voxel MNI coordinates (x, *y*, z)	Region
[Negative emotional cues – neutral emotional cues] > [cocaine cues – neutral cocaine cues]				
<0.001	38,492	>0.99	54, −72, 0	Temporal_Mid_R
		>0.99	42, −48, −18	Fusiform_R
		>0.99	−44, −52, −18	Fusiform_L
		>0.99	48, −82, 4	Occipital_Mid_R
		>0.99	−8, −80, −42	Cerebelum_Crus2_L
		>0.99	8, −78, −38	Cerebelum_Crus2_R
		>0.99	50, 22, 26	Frontal_Inf _R
<0.001	1,391	6.48	−38, 8, 30	Precentral_L
		3.45	−40, −12, 46	Postcentral_L
		5.36	−54, 16, 28	Frontal_Inf_L
<0.001	1,091	4.93	6, 16, 52	Supp_Motor_Area_R
		3.69	−6, 10, 56	Supp_Motor_Area_L
		4.58	0, 40, 52	Frontal_Sup_Medial_L
		3.77	6, 48, 38	Frontal_Sup_Medial_R
[Cocaine cues – neutral cocaine cues] > [negative emotional cues – neutral emotional cues]				
<0.001	1,391	5.32	12, −54, 30	Precuneus_R
		4.43	−2, −64, 36	Precuneus_L
		3.79	−4, −48, 32	Cingulum_Post_L
		3.59	4, −44, 28	Cingulum_Post_R

There were no significant group and or sex difference in the association between emotional cue-reactivity and cocaine cue-reactivity. MNI, Montreal Neurological Institute; FWE, family-wise error.

In contrast to our main hypotheses, no sex-dependent differences in cocaine or emotional cue-reactivity were found when comparing CUs to non-CUs. Exploratory analyses demonstrated trend-significant sex differences in the association between cocaine use severity and cocaine cue-induced activation of the DS and amygdala. Similarly, significant sex differences were demonstrated in the relationship between years of regular use and emotional cue-induced activation of the dACC and VS.

Strikingly, no group differences in neutral cocaine cue-reactivity were found (neither in the ROIs nor other brain regions). This contradicts numerous studies that consistently demonstrated that substance-related cues induce strong activation within the mesocorticolimbic circuit, including the striatum, amygdala, and medial PFC [5]. Indeed, using the same cues in a similar population of male CUs, we did demonstrate strong activation in these brain regions [39]. An important difference between the current study and the previous study is that we applied a block design instead of an event-related design. As block designs are, however, generally associated with more robust brain responses [45], this is unlikely to explain the lack of significant cocaine cue-reactivity in CUs in the current study. Alternatively, 22.6% of the male CUs and 11.5% of the female CUs did not meet the DSM5 criteria for a CUD. As a consequence, this heterogeneity in cocaine use severity might explain the lack of group differences in cocaine cue-reactivity. A more likely explanation for not finding group differences in cocaine cue-reactivity, however, is that in the current fMRI paradigm blocks with cocaine-related cues were alternated with blocks of negative emotional cues. In support of this, various studies demonstrated that stress, aversive, or negative emotional cues attenuate striatal [46, 47], and amygdala activation during reward anticipation [48, 49]. It is suggested that this is specific to populations with psychiatric disorders [49]. Therefore, sex-dependent differences in the neural mechanisms of cocaine cue-reactivity would have been better studied using a separate task as opposed to combining negative emotional and cocaine cues in the same task. Consequently, the current findings on sex-dependent differences in the neural correlates of cocaine cue-reactivity should be taken with caution.

While the current study's main hypotheses for cocaine cue-reactivity were not confirmed, exploratory analyses revealed interesting findings. A trend-significant sex difference in the association between cocaine use severity and cocaine cue-reactivity in the DS and amygdala was found. However, any clinical implications of the sex-dependent relationship between cocaine use severity and cocaine cue-reactivity should be taken with caution because of the (i) lack of group differences in cocaine cue-reactivity in the current study, ii) the fact that sex differences in the association between cocaine use severity and cocaine cue-reactivity findings did not remain significant following a Bonferroni correction.

Second, exploratory analyses revealed significant sex differences in the association between years of regular use and emotional cue-induced activation of the dACC and VS. Follow-up analyses demonstrated that this relationship in both brain regions was significant and negative in female CUs, but absent in male CUs. Previous research has consistently demonstrated decreased neural responses to emotional stimuli in CUD [50, 51], particularly among female CUs in the medial prefrontal cortex/ACC region [11]. This attenuated response to emotional cues is consistent with the impaired response inhibition and salience attribution model [52] in which individuals devalue non-drug-related rewards and negative stimuli that leads to risky behaviors [11] and poor treatment outcome [53]. Moreover, the VS is posited to play a pivotal role in mediating responses to aversive stimuli [53]. Presumably, this is due to the "rewarding effects" of successfully avoiding aversive or punishing events [54, 55], which have been shown to promote future behavior in animals [56]. Consistently, one human study demonstrated decreased activation of the NAc (part of the VS) during passive avoidance in response to aversive stimuli, whereas greater activation of the NAc was found during active avoidance [57]. Taken together, this indicates that female CUs with more years of cocaine use assign less salience toward negative emotional stimuli and are less able to actively avoid aversive stimuli, including the negative consequences of cocaine use, primarily due to hypoactivation in the dACC and VS, respectively. This could make female CUs more prone to risky behavior as the addiction develops with more years of use, which could account for the observed "telescoping effect" in female substance users [2].

Finally, whole-brain analyses revealed significant emotional cue-induced activation of the salience network, including the medial PFC. Moreover, emotional cue-induced activation of the right insula was significantly stronger in CUs compared to non-CUs, but no sex-dependent differences. This is inconsistent with earlier research which demonstrated greater insula activity in female CUs compared to male CUs when exposed to stress cues [12, 13]. Potentially, this could be explained by the particular representation of emotional cues, i.e., negative valence pictures in the current study versus personalized stress imagery in earlier studies [12, 13].

Indeed, personalized cues potentially maximize cue-reactivity, but they simultaneously lead to heterogeneity that limits generalizability and interpretation [58]. Lastly, whole-brain analyses demonstrated that the right insula and amygdala were more strongly activated in females compared to males in response to emotional cues, but there were no significant sex-dependent differences between CUs and non-CUs.

An important strength of the current study is its design to specifically investigate sex differences in both cocaine and emotional cue-reactivity in regular CUs and non-CUs. Specifically, the current study comprised a relatively large sample of non-treatment-seeking CUs, of which the majority met the DSM5 criteria for CUD according to a self-report questionnaire [32]. Moreover, all CUs had a score of 8 or higher on the DUDIT, which is indicative of a SUD [59]. While male and female CUs were matched on most cocaine use-related variables, female CUs were associated with earlier onset of regular cocaine use when compared to male CUs but did not differ significantly in total years of regular use or use per month (in grams). Another strength of the current study is that the negative emotional, and neutral cues were obtained from the OASIS database [38] and the cocaine cues were obtained from an earlier study [39] that facilitates replicability for future research. Lastly, exploratory analyses were performed on the influence of menstrual phase and the use of hormonal contraceptives as there is increasing evidence that fluctuating sex hormones strongly influence processes of positive and negative reinforcement [22, 23]. In line with this, our results suggest that emotional cue-induced activation of the amygdala and DS is moderated by hormonal contraceptive use and menstrual phase, thus highlighting the relevance of including measures of menstrual phase and hormonal contraceptive use in future studies.

One limitation of the current study is its cross-sectional design which precludes the ability to make any conclusions about cause and effect regarding the aforementioned relationships. Furthermore, the current study did not perform a urine screening while participants were instructed to abstain from cocaine use 24 h prior to study participation. This is important as cocaine metabolites can be detected in urine up to 6 days after last use [28], which is much longer than its psychopharmacological effects. Alternatively, the current study used the TLFB prior to the experiment which is a highly reliable method to assess cocaine use [29]. Although several studies show a high concordance between self-report and urine screening [60, 61], it remains impossible to conclude that participants were not (still) intoxicated or inebriated. Another limitation of the current study is the possible presence of withdrawal symptoms in the CUs. As the participants were not daily users, however, it is unlikely that they suffered from cocaine withdrawal. Moreover, as there were no explicit instructions to the participants to abstain from tobacco use and the whole study procedures took approximately 90 min, it is unlikely that the participants experienced withdrawal from nicotine. However, as we did not explicitly test for the presence of withdrawal symptoms, we cannot exclude this possibility. Moreover, analysis based on the clinical cutoff values for the STAI and BDI-II, however, do indicate that of the non-CU group, 6 reported clinical relevant levels of anxiety and 3 reported clinical relevant levels of depression. However, we did not perform a structured clinical interview to diagnose the presence of psychiatric disorders; we cannot exclude the possibility that some of the participants in either the non-drug-using control or CU group, had a psychiatric disorder. Finally, a potential limitation of the applied fMRI task was the relatively short resting period in between blocks. While the periods between blocks in the fMRI paradigm were approximately 12.5 s, they also included the rating of arousal and craving. Hence, these blocks cannot be considered actual resting blocks. This could have contributed to a carryover effect of the different blocks, potentially explaining the lack of significant effects of the cocaine versus neutral cocaine blocks in the CU group. In future, research either longer resting periods between blocks should be applied, or the drug and emotional cue-reactivity paradigms should be applied in different tasks, to circumvent possible carryover effects of reward and emotional cues [58].

To further establish the current findings, future research should take into account duration and severity of use when conducting cue-reactivity paradigms by performing longitudinal and prospective research (e.g., ecological momentary assessments) to gain a better understanding of sex-dependent trajectories in positive and negative reinforcement within the development of CUD. Moreover, understanding sex differences in the neural mechanisms underlying CUD is clinically significant because of potential differential treatment effects in both males and females [7]. For instance, guanfacine is able to elicit a greater reduction in stress- and cue-mediated cocaine craving in female CUs [62] due to improvements in cognitive control [63]. Moreover, oxytocin has shown promise in diminishing the stress response (i.e., less amygdala activation) to cocaine cues in male CUs with a history of childhood trauma, whereas it increased the stress response in female CUs with childhood trauma [64].

In conclusion, the current study found no significant sex differences in cocaine and emotional cue-reactivity in regular CUs. Exploratory analyses did demonstrate significant sex differences in the association between cocaine use severity and cocaine-cue-induced activation of the amygdala and DS. Yet, these findings should be taken with caution due to the lack of significant cue-induced activation of the ROIs in CUs compared to non-CUs. Importantly, years of regular cocaine use were shown to be associated with emotional cue-reactivity in female CUs, but not in male CUs, which may underlie the telescoping effect that has been reported in female substance users. It is important to keep improving our understanding of sex differences in the development of CUD due to its implications for treatment efficacy in both males and females.

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Statement of Ethics

The current study was approved by the Ethics Review Board of the Faculty of Social and Behavioral Sciences, University of Amsterdam (ERB number: 2019-DP-9964). For the screening procedure, participants provided online consent. On the research-testing day, all participants provided written informed consent for study participation.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

A.M.K. was responsible for the study concept, design, data acquisition, analysis. S.T. was responsible for preparing the first draft of the manuscript. A.M.K. and A.E.G. provided critical revision of the manuscript for important intellectual content. E.G.S. was responsible for the supplement. All authors critically reviewed content and approved final version for publication.

Data Availability Statement

The data that support the findings of this study are not publicly available due to privacy reasons but are available from the corresponding author upon request. A preprint version of this article is available on Authorea [64].

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