

The relationship between craving and insular morphometry in regular cocaine users: Does sex matter?

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Funding information

Amsterdam Brain and Cognition Talent Grant

Abstract

While it has been suggested that cocaine use and relapse in women is more strongly related to stress-relief craving, whereas cocaine use in men is more strongly related to reward craving, the neural mechanisms that underlie these differences are poorly understood. The aim of this study was to investigate sex-dependent differences in insular morphometry and associations with craving, in a sample of regular cocaine users (CUs) and non-drug using controls (non-CUs). It was hypothesized that insular volume, thickness and surface area would be lower in CU women, compared with CU men and non-CUs. It was furthermore hypothesized that insular morphometry, particularly insular thickness, would be negatively associated to reward craving in CU men, while being negatively associated with stress-relief craving in CU women. In contrast to the hypothesis, we did not find evidence of sex-specific differences in insular morphometry in CUs. However, sex-specific association between stress-relief craving and insular morphometry were found: Right insular volume was negatively associated with stress-relief craving in CU women, whereas this association was positive in CU men. Additionally, right insular surface area was negatively associated with stress-relief craving in cocaine-using men, whereas this association was positive in cocaine-using women. In conclusion, the current study provides first evidence of sex-specific differences in the association between craving and insular morphometry in a sample of regular cocaine users. Although speculative, these sex-specific alterations in insular morphometry may underlie higher stress-induced craving and relapse in CU women compared with CU men.

KEYWORDS

cocaine use disorder, craving, insula, sex and gender differences, stress

1 | INTRODUCTION

Cocaine is one of the most commonly used illicit drug in Europe, and the prevalence of (high-risk) use has been increasing in the past decade.¹ While the prevalence of cocaine use is approximately two to

three times higher in men than in women (in the Netherlands, 1.2% of men, and 0.4% of women report recent use of cocaine) this gap is slowly closing.² Research furthermore suggests that women progress more rapidly to cocaine use disorders (CUDs) than men and show greater rates of relapse.³ Nonetheless, very little is known about sex

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or gender differences in the mechanisms involved in the development and treatment of CUD.³

A central theory in addiction research is that the development of problematic substance use results from a shift in positive reinforcement (i.e., reward-driven craving and use) to negative reinforcement (stress-relief driven craving and use).⁴ While research is limited, there are some indications that the prevalence of stress-induced relapse is higher in women compared with men with a CUD.³ For example, women with a CUD generally report stronger subjective (craving and negative affect) and physiological responses to stress-related cues compared with drug-related cues, whereas men generally show stronger subjective and physiological responses to drug-related cues compared with stress-related cues.⁵⁻⁷ It has furthermore been suggested that subjective stress-related factors are more predictive of relapse to substance use in women than in men.^{8,9} Unfortunately, the neural mechanisms that underlie these sex and gender differences in craving and relapse in CUD are still poorly understood.

A key structure involved in craving is the insula, a brain region involved in multiple bodily functions, including interoception and emotional processing.¹⁰ Within the context of substance use disorders (SUDs), the insula is involved in the conscious awareness of the aversive bodily feelings that constitute the craving response¹¹ and is therefore suggested to be specifically involved in stress-induced craving and relapse.^{10,12} Associations between craving and insula function or structure have been found in several SUD populations, including heroin use disorder,¹³ alcohol use disorder,¹⁴ tobacco use disorder^{15,16} and cannabis use disorder.¹⁷ In CUD, it has been shown that craving for cocaine is positively associated with insula activation in response to drug-related cues^{18,19} and negatively associated with perfusion and volume of the insula.²⁰ Although these studies underline that the insula is crucially involved in craving and substance use, sex or gender differences in the association between insula functioning and craving in CUD is still scarcely investigated.

Research did demonstrate that women with a CUD show stronger stress-related activation of the insula,^{6,21} whereas men with a CUD show stronger drug-reward related activation of the insula.^{6,22} These studies support the hypothesis that women with a CUD may be more prone to stress-relief craving, whereas men are more prone to reward craving, which may be related to sex or gender differences in insular functioning. However, whether these differences in the relationship between insular activation and craving are paralleled by sex or gender differences in insular morphometry is less well understood. Using voxel-based morphometry (VBM) or surface-based analyses (SBA), it has been demonstrated that cocaine using men have lower insular grey matter volume (GMV) compared with non-drug using men.²³⁻²⁵ Lower insular GMV has furthermore been suggested to be specifically and dose-dependently related to the use of cocaine, and not to other substances.²⁶ Insular morphometry in individuals with a CUD has furthermore been shown to be dependent on sex or gender: Insular volume^{27,28} and thickness²⁹ is found to be lower in CUD women compared with CUD men. Research in nicotine dependent individuals furthermore demonstrated that cortical thickness in the right insula is negatively correlated with craving for cigarettes,³⁰ and

recent research showed that this negative association between cortical thickness of the insula and craving may be particularly strong in women that smoke cigarettes.³¹ Although these studies suggest that interventions that specially target insular function and structure, such as brain stimulation of the insula,³² may be particularly effective in the treatment of CUD in women,³¹ sex and gender differences in the association between insular morphometry and craving has not been investigated in cocaine users yet.

The aim of the current study, therefore, was to explore sex differences in the relationship between insular morphometry and craving in a sample of nontreatment-seeking regular cocaine users (CUs), suspected of having a CUD, and non-drug using controls (non-CU) using SBA. Based on previous literature, it was expected that insular thickness, surface area, and volume is smaller in CU women compared with CU men, non-CU women, and non-CU men. We furthermore expected insular morphometry, particularly CT, to be negatively associated to reward craving (and not relief craving) in CU men, while we expected insular morphometry, particularly insular thickness, to be negatively associated with relief craving (and not reward craving) in CU women.

2 | MATERIALS AND METHODS

2.1 | Participants

This study is part of a large project designed to investigate the role of sex in the neurocognitive mechanisms underlying CUD.³³ In total, 58 CUs (31 men/27 women) and 56 matched non-drug using controls (non-CUs) (28 men/28 women) were included in this study. All cocaine users were actively using at the time of assessment and were nontreatment seeking. The participants were recruited through social media and local advertisement in the Amsterdam area, the Netherlands. CUs used cocaine (intranasally) at least four times a month in the past 6 months. Non-CUs were excluded if they were an active smoker, had an Alcohol Use Disorders Identification Test score > 12 (AUDIT³⁴), used cocaine more than five times in their life, or used illicit substances more than five times in the past 6 months. Both CUs and non-CUs were excluded when there was an indication of post-traumatic stress disorder based on a score of 2 or higher on the PTSS Jellinek Screening Questionnaire.³⁵ All participants provided informed consent and received a monetary compensation. This study was approved by the Ethics Review Board of the Faculty of Social and Behavioral Sciences, University of Amsterdam (ERB number: 2019-DP-9964). Note: Sex in the current study was operationalized by asking: Are you a 'man', 'woman', 'other'? While none of the participants identified as 'other', we did not specifically differentiate between sex assigned at birth (male, female, intersex) and gender-identity (women, man, transgender, a gender not listed). As a consequence, the reported differences between men and women can either reflect biological sex differences, socio-cultural gender differences, or more likely reflect a combination of both. For simplicity, however, we will refer to the reported differences between men and women as sex-differences throughout the remainder of the publication.

2.2 | Assessment of substance use and psychological functioning

In all participants, alcohol use in the 28 days prior to study participation was assessed using the time-line follow-back procedure,³⁶ and alcohol use severity was measured using the Alcohol Use Disorders Identification Test score.³⁴ Gross monthly joint income and education level was assessed with an in-house questionnaire. Moreover, the Beck Depression Inventory (BDI)³⁷ and State and Trait Anxiety Inventory (STAI-trait)³⁸ were applied to assess the presence of depressive and anxiety disorders, based on clinical cut-off scores. For the BDI, scores below 13 indicate the absence of a depression; scores between 14 and 19 indicate the presence of a mild depression; scores between 20 and 28 indicate the presence of a moderate depression; and a score above 29 indicates the presence of a severe depression.³⁷ For the STAI-trait, a cut-off point of 40 is normally used for clinically significant symptoms of trait anxiety.^{39–41} The following characteristics of substance use were assessed in CUs only: Severity of cocaine use and related problems in the past 12 months was assessed using the Drug Use Disorder Identification Test for cocaine (DUDIT⁴²); cocaine and cannabis use in the 28 days prior to study participation was assessed using the Time Line Follow-Back procedure;³⁶ and age of onset of regular use was assessed using an in-house questionnaire.* Years of regular use was computed by subtracting age of onset of regular use from the current age. Moreover, smoking behaviour (number of smoking days per week and cigarettes per day) was assessed using an in-house questionnaire, and severity of cannabis use was assessed using the Cannabis Use Disorder Identification Test-Revised.⁴³ Current DSM-5 symptoms for CUD, cannabis use disorder and AUD were assessed using a self-reported questionnaire based on the SCID.⁴⁴

2.3 | Structural magnetic resonance imaging acquisition and processing

The structural magnetic resonance imaging (MRI) images were acquired on a 3 T Philips Achieva DS scanner with a 32 channel head coil. Three-dimensional T1-weighted images were made using the following parameters: repetition time (TR) = 8.24 ms, echo time (TE) = 3.8 ms, voxel size = $1 \times 1 \times 1 \text{ mm}^3$, scan resolution = $240 \times 240 \text{ mm}$, transverse slices, 8° flip angle.

Data were preprocessed using fMRIPrep 1.3.2, which incorporates many recommended practices for fMRI preprocessing as well as running the FreeSurfer pipeline (version 6.0.1): The T1-weighted (T1w) image was corrected for intensity non-uniformity (INU) with N4BiasFieldCorrection, distributed with ANTs 2.2.0 (RRID:SCR_004757), and used as T1w-reference throughout the workflow. The T1w-reference was then skull-stripped with a Nipype implementation of the antsBrainExtraction.sh workflow (from ANTs), using OASIS30ANTs as target template. Brain surfaces were reconstructed using recon-all (FreeSurfer 6.0.1, RRID:SCR_001847), and the brain mask estimated previously was refined with a custom variation of the method to reconcile ANTs-derived and FreeSurfer-derived

segmentations of the cortical grey matter of Mindboggle (RRID:SCR_002438). Spatial normalization to the ICBM 152 Nonlinear Asymmetrical template version 2009c (RRID:SCR_008796) was performed through nonlinear registration with antsRegistration (ANTs 2.2.0), using brain-extracted versions of both T1w volume and template. Brain tissue segmentation of cerebrospinal fluid (CSF), white-matter (WM) and grey matter (GM) was performed on the brain-extracted T1w using fast (FSL 5.0.9, RRID:SCR_002823). Of each participant, CV, SA, and CT of the Insula and total intracranial volume (ICV) were calculated. Regions of interest (ROIs) were defined using the Desikan–Killiany atlas implemented in FreeSurfer.

2.4 | Statistical analysis

All analyses were performed using SPSSV25.

Within the CU group, sex differences in demographic and/or drug-related variables were compared using two-way ANOVAs, Mann–Whitney *U* tests or χ^2 tests, when appropriate. Sex differences were tested for age, alcohol use (units of alcohol per month), alcohol use severity, onset of regular cocaine use, cocaine use (grams/month), cigarette use (cigarettes/month), alcohol use (units/month), cannabis use (joints/month), DDQ (sub)scores, DUDIT scores, and DSM-5 classification for SUDs. Values are given in mean \pm standard deviation or median \pm IQR for normally and non-normally distributed data, respectively. In case of significant differences between CU men and women on one of these demographic or clinical variables, sensitivity analyses were performed to test if including this potential confounder as covariate of non-interest in the subsequent analyses, changed the results.

The differences in insular morphometry between groups, sex and the interaction between these two were investigated using two-way ANCOVAs, with insular volume, thickness and surface area (left and right separately) as dependent variables, and age and ICV as covariates of non-interest. Significant interaction effects were followed up with within group/sex follow-up tests.

To assess the relationship between the scores of the Desire for Drug Questionnaire and insular morphometry and sex difference herein, multiple hierarchical linear regression analyses were applied on insular volume, thickness and surface area (left and right). In each analysis, age and ICV were entered as covariates of non-interest in the first step, in the second step the DDQ subscales (craving related to desire, negative reinforcement and loss of control) and sex were entered, and in the third step the sex * DDQ interaction term for each subscale was entered. If significant interaction terms were present, follow-up within sex regression analyses were performed. All continuous regressors were standardized before entering them in the regression model. Because some assumptions of a linear regression analysis were violated, all significance values were bootstrap corrected using 1000 bootstrapping iterations.

Methods and results regarding exploratory analyses on sex differences in the association between substance use and insular morphometry are reported in the supporting information.

3 | RESULTS

3.1 | Demographic and clinical variables

There were no significant sex, group or sex by group interaction effects on age, educational level or gross monthly income. There were, however, significantly more CUs with a BDI score that indicated the presence of a mild to severe depression, but no sex or sex by group differences were detected. Based on the STAI-trait scores there were no sex, group or sex by group interaction effects on the presence of clinically relevant anxiety symptom severity (Table S1). Within the CU group, age of onset of regular cocaine use was significantly higher in men (23.0) compared with women (21.0), but there were no differences in years of regular use (3 years for both men and women), cocaine use (women: 3.4 g/month, men: 4.1 g/month), cocaine craving, or other substance use characteristics. The average DUDIT scores (for cocaine use), were 15.5 (range: 10–28) in CU women, and 16.0 (range: 8–29) in men, which is indicative of severe cocaine related problems.⁴³ In line with this, 80% of the CU men and 88.5% of CU women met the DSM-5 criteria for a mild, moderate or severe CUD. Comorbid alcohol use was high in CU women and men, with an alcohol intake of 63.5 and 75.0 glasses per month and an AUDIT score of 12.5 and 10.0, respectively. In addition, 73.1% of all CU women and 80% of all CU men met the DSM-5 criteria for a mild, moderate or severe AUD. Comorbid cannabis use was much less frequent, with 15.4% of all CU women and 30.0% of all CU men meeting the DSM-5

criteria for a mild, moderate or severe cannabis use disorder. See Table S2 for detailed substance use characteristics and statistics.

3.2 | Group and sex differences in insular morphometry

While on average cortical thickness, surface area and volume was smaller in CUs than in non-CUs, none of these differences were significant. Cortical thickness of the left insula was significantly smaller in women than in men (Table 1), but no such sex differences were found for right insular thickness, nor for bilateral insula volume or surface area. In contrast to our hypothesis, no group by sex interaction was found for cortical morphometry of the left or right insula (Table 1).

3.3 | Sex differences in the association between insular morphometry and craving

To assess if there were sex differences in the relationship between insular morphometry and craving, six hierarchical regression analyses were performed, for thickness, surface area and volume of the left and right insula separately. In Step 1, the potential confounders age and ICV were included; in Step 2, the main effects of sex are craving related to negative reinforcement (DDQ relief), craving related to loss of control (DDQ control) and craving related to desire (DDQ desire);

TABLE 1 Group and sex differences in insular grey matter (GM) volume, cortical thickness (CT) and surface area (SA)

	Non-CU		CU		Group effect	Sex effect	Group × sex interaction effect
	Women (n = 27)	Men (n = 28)	Women (n = 26)	Men (n = 30)			
Insular morphometry							
Grey matter volume (left)	7414 ± 664	8390 ± 886	7192 ± 747	7916 ± 824	$F_{1,105} = 2.56$, $p = 0.11$, $\eta^2 = 0.02$	$F_{1,105} = 0.41$, $p = 0.52$, $\eta^2 < 0.01$	$F_{1,105} = 0.16$, $p = 0.69$, $\eta^2 < 0.01$
Grey matter volume (right)	7349 ± 679	8258 ± 818	7036 ± 701	7868 ± 851	$F_{1,105} = 3.29$, $p = 0.07$, $\eta^2 = 0.03$	$F_{1,105} < 0.05$, $p = 0.94$, $\eta^2 < 0.01$	$F_{1,105} = 0.03$, $p = 0.86$, $\eta^2 < 0.01$
Cortical thickness (left)	3.16 ± 0.15	3.26 ± 0.14	3.16 ± 0.15	3.16 ± 0.17	$F_{1,105} = 1.44$, $p = 0.23$, $\eta^2 = 0.01$	$F_{1,105} = 0.43$, $p = 0.51$, $\eta^2 < 0.01$	$F_{1,105} = 2.25$, $p = 0.14$, $\eta^2 = 0.02$
Cortical thickness (right)	3.15 ± 0.15	3.23 ± 0.17	3.17 ± 0.15	3.18 ± 0.15	$F_{1,105} = 0.02$, $p = 0.89$, $\eta^2 < 0.01$	$F_{1,105} = 7.96$, $p < 0.01$, $\eta^2 = 0.07$	$F_{1,105} = 1.38$, $p = 0.24$, $\eta^2 = 0.01$
Surface area (left)	2210 ± 234	2417 ± 265	2116 ± 229	2346 ± 311	$F_{1,105} = 1.12$, $p = 0.29$, $\eta^2 = 0.01$	$F_{1,105} = 0.02$, $p = 0.88$, $\eta^2 < 0.01$	$F_{1,105} = 0.36$, $p = 0.56$, $\eta^2 < 0.01$
Surface area (right)	2214 ± 283	2407 ± 294	2072 ± 231	2316 ± 315	$F_{1,105} = 2.7$, $p = 0.10$, $\eta^2 = 0.03$	$F_{1,105} = 2.13$, $p = 0.15$, $\eta^2 = 0.02$	$F_{1,105} = 0.96$, $p = 0.36$, $\eta^2 < 0.01$

Note: Data are in adjusted means ± adjusted standard deviation. Cortical thickness is in millimetres (mm), surface area is in square millimetres (mm²) and grey matter volume is in cubic millimetres (mm³). Three participants were excluded due to outlying morphological values, that is, values below $Q1 - 1.5 \times IQR$ or above $Q3 + 1.5 \times IQR$.

Abbreviation: CU, cocaine user.

and in Step 3, the three interaction terms are sex * DDQ relief, sex * DDQ control and sex * desire. These analyses revealed that craving related to relief craving was negatively related to cortical thickness and cortical surface area of the left insula (Table 2). Additionally, the association between craving related to relief craving and volume of the right insula as well as the association between craving related to loss of control and right insular surface area, were significantly moderated by sex (Table 2, Figure 1). Planned within sex follow-up regression analyses, demonstrated that the association between craving related to relief craving and right insular volume was negative in women ($\beta = -0.34, p = 0.20$) but positive in men ($\beta = 0.31, p = 0.21$). In contrast, the association between craving related to loss of control and surface area of the right insula was positive in women ($\beta = 0.25, p = 0.19$) and negative in men ($\beta = -0.19, p = 0.08$). None of the other main or interaction effects were significant (Table 2, Figure 1).

Because there was a slight difference in age of onset of regular cocaine use between men and women, the analyses were repeated with age of onset included in the first step of the hierarchical regression. After including age of onset as covariate in the analysis, the significant interaction between sex and craving related to relief craving

on cortical volume of the right insula was changed from $\beta = 0.43$ ($p = 0.045$) to $\beta = 0.40$ ($p = 0.08$). Similarly, the significant interaction between sex and craving related to loss of control on surface area of the right insula was changed from $\beta = -0.31$ ($p = 0.04$) to $\beta = -0.31$ ($p = 0.06$). The other significant findings were not altered by including age of onset as a covariate in the analysis. Age of onset was unrelated to any measure of insular morphometry (Note: data on age of onset was missing for three participants; hence, these analyses were based on a sample size of $n = 53$ instead of $n = 56$).

3.4 | Sex differences in the association between insular morphometry and substance use

Exploratory analyses regarding sex difference in the association between substance use and insular morphometry, demonstrated sex differences in the association between cannabis use and surface area of the left insula, as well as sex difference in the association between cigarette use and volume/surface area of the right insula. These results, including the discussion, can be found in the supporting information.

TABLE 2 Multiple regression analysis on the grey matter (GM) volume, cortical thickness (CT) and surface area (SA) of the left and right insula

	Dependent variable					
	Grey matter volume		Cortical thickness		Cortical surface area	
	Left	Right	Left	Right	Left	Right
Step 1: covariates of non-interest						
Age	-0.27**	-0.21*	-0.37**	-0.31*	-0.10	-0.12
ICV	0.69***	0.71***	0.17	-0.05	0.63***	0.67***
R ²	0.55	0.54	0.14	0.10	0.40	0.46
F	32.21***	31.29***	4.22*	2.88	17.95***	22.67
Step 2: main effects sex and craving for cocaine						
Sex	-0.014	0.04	0.10	0.29	-0.07	-0.09
DDQ relief	0.07	0.45	-0.48**	-0.21	0.32*	0.12
DDQ control	0.01	-0.05	-0.24	-0.18	0.09	0.014
DDQ desire	-0.17	-0.12	0.17	-0.005	-0.28	-0.11
R ²	0.57	0.55	0.34	0.20	0.47	0.47
F change	0.49	0.26	3.66*	1.50	1.57	0.31
Step 3: interaction effects sex and craving for cocaine						
DDQ relief * sex	0.14	0.43 ^a	0.10	0.11	0.11	0.32
DDQ control * sex	-0.10	-0.24	0.16	0.19	-0.15	-0.31 ^a
DDQ desire * sex	-0.14	-0.34	0.09	0.24	-0.13	-0.39
R ²	0.57	0.61	0.36	0.25	0.48	0.53
F change	0.25	2.20	0.51	1.18	0.31	1.89

Note: Multiple associations were found between various DDQ measures and insular morphology, including a significant interaction effect with sex. Reported are the standardized beta coefficients. $N = 56$. Bootstrapped p values are reported.

Abbreviation: ICV, intracranial volume.

^aThese findings became non-significant after including onset age of regular use as covariate in the analysis.

* $p < 0.05$. ** $p < 0.01$. *** $p < 0.001$.

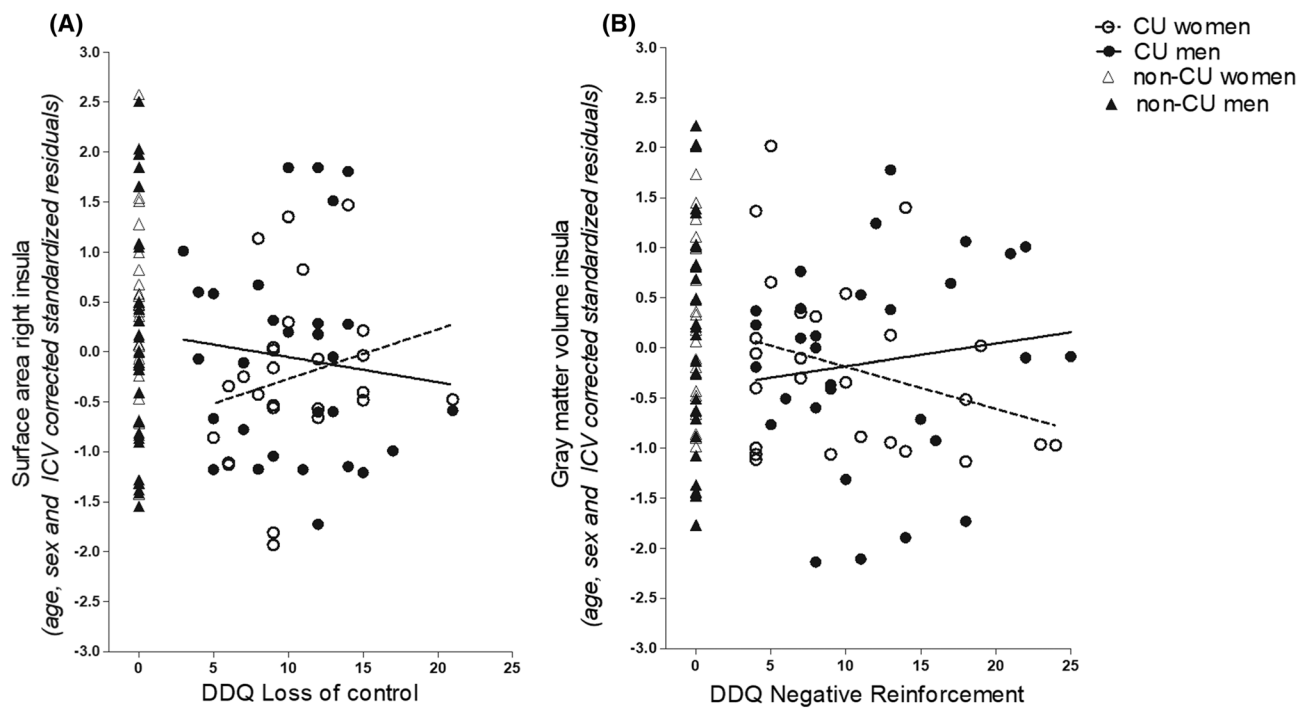


FIGURE 1 The association between craving related to the loss of control and surface area of the right insula (A) was negative in cocaine using men, but positive in cocaine using women. On the contrary, the association between craving related to negative reinforcement and volume of the right insula (B) was positive in cocaine using men, but negative in women. CU, cocaine user

4 | DISCUSSION

Although it has been suggested that negative relief craving is more strongly involved in cocaine use and relapse in women than in men,^{3,5,8,9} sex differences in the neural mechanisms that may underlie these differences have not been investigated thoroughly. The aim of the current study, therefore, was to explore whether there are sex differences in the association between (reward and relief) craving and insular morphometry, as this brain region has been strongly implicated in the involvement of craving.^{10,45–47} It was hypothesized that insular morphometry, specifically GMV, cortical thickness (CT) and cortical surface area (SA), would be more strongly compromised in CU women than CU men, compared with men and women that did not use cocaine. It was furthermore hypothesized that insular morphometry, particularly CT, would be negatively associated to reward craving (and not relief craving) in CU men, while we expected insular morphometry, particularly CT, to be negatively associated with relief craving (and not reward craving) in CU women.

Although insular GMV, SA and CT was overall lower in CUs compared with non-CUs, and left insular thickness seemed to be more strongly affected in CU men compared with CU women, these differences were non-significant. This is in contrast to earlier studies that demonstrated lower GMV specifically in women with a cocaine use disorder,²⁷ stimulant use disorder,²⁸ or substance use disorder (including stimulants, nicotine, alcohol, heroin and cannabis).²⁹ These differences in findings could partially be explained by the fact that previous

studies included abstinent patients, whereas here we report findings of active users of cocaine (non-abstinent). Indeed, it has been suggested that (sub)cortical atrophy in (poly)substance users may be underestimated due to neuroinflammation in response to recent use of substances.^{48–50} As such, sex-specific alterations in insular morphometry may be more pronounced in abstinent substance users, including cocaine users, which could explain the absence of significant sex-specific differences in insular morphometry between cocaine user and non-drug-using controls. Another explanation is that cocaine use in the current population may have been less severe and for a shorter duration compared with the use reported in earlier studies.^{27–29} Indeed, women are suggested to be more susceptible to the neurotoxic effects of stimulants including cocaine.⁵¹ It is therefore not unlikely that sex differences in insular morphometry are more pronounced with longer and more severe use of cocaine.

In the current study, we did demonstrate significant associations between insular morphometry and craving in CUs: Stress-relief craving was negatively associated with left insular CT, and positively associated with left insular SA. CT and SA are two biologically distinct determinants of GMV, and both have their own cellular mechanisms and genetic underpinning.^{52,53} Hence, CT and SA carry unique and complementary information regarding the insular morphometry and function. The current observation that insular thickness is negatively associated with craving is in line with previous research in cigarette smokers.^{30,31} Thinner insular cortex^{54–56} and smaller insular volume^{25,56,57} has furthermore been associated with heightened impulsive and compulsive

behaviour. Hence, insular thinning may be a biomarker for impaired emotion regulation and, as a consequence, enhanced craving. The observation that craving is positively associated with SA of the insula has not been found before. While it may seem conflicting that stress-relief craving was negatively associated with insular CT, but positively associated with insular SA, an inverse relationship between CT and SA is often found in both clinical as nonclinical populations.⁵⁸ This inverse relationship can be explained by the 'balloon model hypothesis' that suggests that this inverse relationship is the result from white matter growth that stretches the cortex tangentially to the pial surface, resulting in thinner cortices.⁵⁹ It has furthermore been suggested that these increases in insular SA in combination with the decreases in insular CT may result in inefficient cognitive control functions.⁶⁰ Hence, smaller insular CT in addition to larger insular SA may predispose to the development of CUD by increasing the risk of stress-driven craving cocaine use. Altogether, these findings corroborate existing evidence that the insula is critically involved in craving and as such the development and maintenance of substance use disorders, including cocaine use disorder.^{10,11,13–20,45–47}

Importantly, the association between stress-relief craving and right insular GMV was significantly moderated by sex: Although the association was negative in CU women, this association was positive in CU men. Although we expected these sex differences to be particularly pronounced in insular CT, these findings are in line with previous research that demonstrated that abstinence induced craving is negatively related to insular CT in nicotine dependent women, but positively related to insular CT in nicotine dependent men.³¹ Lower insular volume, which is the product of insular thinning and reductions in surface area, has shown to be related to impaired attentional control in cocaine users.²⁵ In addition, we also found that craving related to loss of control and right insular SA was also moderated by sex: There was a positive association between right insular SA and craving related to loss of control in CU women, whereas this association was negative in CU men. In combination with previous research, these current findings suggest that stress-related craving (and potentially relapse) in CU women may be particularly driven by alterations in insular morphometry, which could guide the way for the development of sex-specific treatment strategies.

An intriguing finding of the current study was that the sex differences in the association between craving and insular morphometry were shown only for the right insula. Existing literature suggests that the right insula, compared with the left insula, is more strongly involved in the attentional systems of the brain,^{61–63} the processing of negative emotional information⁶⁴ and the hedonic evaluation and motivational approach of rewarding stimuli.⁶⁵ As such, it may not be surprising that sex differences in the relationship between craving and insular morphometry are found only in the right insula. While these findings need to be replicated, an important implication would be studies and interventions that specifically target insular functioning should take laterality of the insula into account. One possible sex-specific treatment strategy could be brain stimulation of the insula.^{32,66} Unfortunately, brain stimulation studies for addiction have mainly targeted the prefrontal cortex, and evidence for the

effectiveness of insular stimulation is lacking. At this point, there has been one published study on the effectiveness of transcranial magnetic stimulation (TMS) of the lateral prefrontal cortex and insular cortex, demonstrating reduced relapse rates in smokers that underwent active TMS treatment.⁶⁷ Importantly, the insula does not have to be specifically targeted with stimulation in order to restore in function. For example, deep brain stimulation (DBS) of the ventral anterior limb of the internal capsule showed to restore insular function in patients with an obsessive compulsive disorder⁶⁸ while DBS of the thalamus showed to increase volume of several brain regions, including the insula, in patients with disorders of consciousness.⁶⁹ Altogether there is promising evidence that either direct or indirect stimulation of the insula could be effective in the treatment of substance use disorder.^{32,66} Although speculative, the findings of the current study suggest that insular stimulation may be particularly effective in the treatment of women.

To our knowledge, this is the first study to demonstrate sex differences in the relationship between craving and insular morphometry in regular cocaine users, providing a possible underlying mechanism of higher stress-induced cocaine use and relapse in women compared with men. Importantly, this study was specifically designed to assess sex differences in the neural mechanisms involved in cocaine use disorder,³³ and therefore, cocaine-using men and women were well matched on important variables including age and most cocaine use characteristics. Nonetheless, women reported to have started regular cocaine use at a slightly earlier age than men did (although years of regular use did not differ between men and women). As such, all analyses were repeated correcting for these differences in age of onset of regular use. After doing so, the sex by craving interaction effects on right insular GMV and SA slightly changed from significant to trend-significant. However, these analyses were based on a sample size of $n = 53$ instead of $n = 56$ because data for age of onset were missing in three participants. Moreover, the effect sizes remained similar in the analyses correcting for age of onset. This suggests that the slight change in significant values is a consequence of a reduction in power. Altogether, this implies that sex differences in the relationship between craving and insular morphometry are not explained by age of onset, although this should be replicated using a larger sample size. Moreover, while a relatively large sample of 56 cocaine users and 55 non-drug-using controls were included, this sample size was only enough to detect relatively large effect sizes with regard to sex differences in the association between craving and insular morphometry. Hence, more subtle differences may have been missed. As such, the current findings warrant replication in a larger sample. Furthermore, we instructed participants to abstain from cocaine for 24 h prior to study participation. We did not perform a urine screening to check this as cocaine metabolites can be detected in urine up to 6 days after the last use in regular CUs,⁷⁰ which is much longer than its psychopharmacological effects. Instead, we used the time-line follow-back procedure to assess cocaine (and other substance) use prior to the experiment, which is generally considered to be a highly reliable method to assess information about substance use, including cocaine use, in both treatment- and nontreatment-seeking populations.⁷¹

Nonetheless, we cannot fully exclude the possibility that sex differences in recent cocaine use may have biased the findings. A last limitation of the current study is that we only tested for sex differences in insular morphometry, without taking into account gender. According to the Sex and Gender Equity in Research (SAGER) guidelines, gender is an equally important determinant of health and well-being as sex.⁷² While the terms sex and gender are often confused in scientific literature, gender refers to the socially constructed roles, behaviours and identities of female, male and gender-diverse people whereas sex refers to a set of biological attributes in humans and animals that are associated with physiological features. As such, future research should take gender as a potential moderating factor in the (neuro)pathology of addiction into account, for example, by calculating a gender index based on a variety of psychosocial gender-related variables.⁷³

In conclusion, the current study provides important evidence of sex-specific differences in the association between craving and insular morphometry in a sample of regular cocaine users. Although speculative, these findings may reveal a potential mechanism that underlies higher stress-induced craving, cocaine use and potential relapse in women compared with men, which may be mediated by sex-specific alterations in insular morphometry.

ACKNOWLEDGMENTS

The authors would like to thank Nutsa Nanuashvili, Daantje de Bruin and Annel Koomen for their assistance in data collection.

FUNDING INFORMATION

The project was funded by an Amsterdam Brain and Cognition Talent Grant.

CONFLICT OF INTEREST

None of the authors reported biomedical financial interests or potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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ENDNOTE

* As eight subjects in the CU group lacked TLFB data, alcohol and cannabis in these participants were estimated by multiplying the Items

1 and 2 of the AUDIT and Cannabis Use Disorder Identification Test Score - Revised (CUDIT-R) respectively.⁷⁴ Cocaine use was estimated based on an in-house questionnaire that was applied during screening.

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SUPPORTING INFORMATION

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How to cite this article: Abdel Malek GS, Goudriaan AE, Kaag AM. The relationship between craving and insular morphometry in regular cocaine users: Does sex matter? *Addiction Biology*. 2022;27(2):e13157. doi:10.1111/adb.13157