

# Sex-dependent prefrontal cortex activation in regular cocaine users: A working memory functional magnetic resonance imaging study

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## Abstract

Although two thirds of patients with a cocaine use disorder (CUD) are female, little is known about sex differences in the (neuro)pathology of CUD. The aim of this explorative study was to investigate sex-dependent differences in prefrontal cortex (PFC) functioning during a working memory (WM) functional magnetic resonance imaging (fMRI) task in regular cocaine users (CUs), as PFC deficits are implicated in the shift from recreational cocaine use to CUD. Neural activation was measured using fMRI during a standard WM task (n-back task) in 27 male and 28 female CUs and in 26 male and 28 female non-cocaine users (non-CUs). Although there were no main or interaction effects of sex and group on n-back task performance, WM-related (2-back > 0-back) PFC functioning was significantly moderated by sex and group: female compared with male CUs displayed higher WM-related activation of the middle frontal gyrus (MFG), whereas female compared with male non-CUs displayed lower WM-related MFG activation. Additionally, WM-related activation of the inferior frontal gyrus, insula, and putamen was negatively associated with cocaine use severity in female but not male CUs. These data support the hypothesis of sex-dependent PFC differences in CUs and speculatively suggest that PFC deficits may be more strongly implicated in the development, continuation, and possibly treatment of CUD in females. Most importantly, the current data stress the importance of studying both males and females in psychiatry research as not doing so could greatly bias our knowledge of CUD and other psychiatric disorders.

## KEYWORDS

cocaine, gender differences, prefrontal cortex, sex differences, substance use disorder, working memory

## 1 | INTRODUCTION

Cocaine is one of the most commonly used illicit drugs in Europe, and the prevalence of use has increased in the past decade.<sup>1</sup> Although the

prevalence of cocaine use is 2–3 times higher in men than in women, this gap is slowly closing.<sup>2</sup> Although women start using cocaine at a later age, they are suggested to progress more rapidly to compulsive use and have higher relapse rates compared with men.<sup>3</sup> A better

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understanding of the role of sex in the (neuro)pathology of cocaine use disorder (CUD) could pave the way for the development of sex-tailored treatment strategies.<sup>4</sup>

The prefrontal cortex (PFC) plays a key role in cognitive control and emotion regulation, and compromised PFC functioning is thought to promote the shift from recreational to compulsive drug use.<sup>5</sup> The few studies that investigated the role of sex in CUDs showed lower dorsomedial and ventromedial PFC activity in female compared with male cocaine users (CUs) during cocaine cue imagery<sup>6</sup> and in response to negative emotional<sup>7</sup> and drug-salient stimuli.<sup>8</sup> In contrast, female CUs also showed higher dorsomedial PFC activity in response to negative emotional stimuli.<sup>9</sup> Moreover, pharmacological enhancement of PFC functioning (using the noradrenergic  $\alpha$ 2-receptors agonist guanfacine) mitigated stress-induced arousal and craving<sup>10,11</sup> and improved cognitive control<sup>12</sup> in CUD females, but not males. These studies suggest that PFC functioning is specifically impaired in females with a CUD in the context of emotionally salient stimuli, but it remains to be tested if these results generalize to cognitive control-related processes.

Working memory (WM) refers to the ability to temporarily maintain, update, or manipulate information in an active state and is crucially involved in cognitive control.<sup>13,14</sup> WM performance is generally associated with activation of a network of various PFC and parietal brain areas, with increased WM load being associated with increased activation.<sup>13</sup> In various psychiatric disorders, stronger WM-related (high WM load > low WM load) PFC activation (compared with a control population) is suggested to reflect compensatory but inefficient neural information processing, leading to deficits in WM performance.<sup>15</sup>

WM tasks generally require sustained attention, information storage, memory for temporal order as well as the updating and manipulation of information.<sup>16,17</sup> As such, WM-related differences in neural activation in CUD populations may reflect differences in any of these functions. Neuroimaging research demonstrated WM-related PFC deficits in CUD, although both higher WM-related PFC activation (middle frontal gyrus [MFG])<sup>18</sup> and lower PFC activation (cingulate gyrus, middle, superior, and inferior frontal gyrus)<sup>19</sup> have been reported. Research in other substance use disorders (SUDs) reported similar mixed findings, including WM-related (dorsomedial) PFC over-recruitment in alcohol use disorder (AUD) patients<sup>20</sup> and cannabis users.<sup>21</sup> Moreover, higher WM-related (dorsolateral) PFC activity has been reported to predict cannabis use.<sup>22-24</sup> In contrast, lower WM-related PFC activation (middle and superior frontal gyrus, precentral and postcentral gyrus) has also been demonstrated in AUD patients,<sup>25,26</sup> with lower WM-related activation of the rostral PFC and ventrolateral PFC predicting relapse to alcohol use.<sup>27</sup>

A possible explanation of previous conflicting findings could be that the majority of these studies did not account for sex differences. Although most neuroimaging WM meta-analyses in nonsubstance using populations did not include sex in their analyses, a 2014 meta-analysis demonstrated higher WM-related limbic and (middle and medial) PFC activity in females but higher WM-related parietal activity in males.<sup>28</sup> As such, omitting sex from the analyses could greatly

obscure the interpretation of WM-related neural deficits in psychiatric disorders, including CUD.<sup>29</sup>

To date, only one study reported on sex differences in WM-related PFC activation in CUD.<sup>19</sup> Although this study did not demonstrate any significant group (CUD vs. controls) by sex interaction effects on WM-related PFC activation, this was likely due to insufficient statistical power (i.e., inclusion of three female vs. 16 male CUD patients). Based on the earlier described findings of lower dmPFC activation during the processing of emotionally salient stimuli in female compared with male CUD patients,<sup>6-8</sup> and the finding that pharmacological enhancement of PFC functioning improved cognitive control while reducing arousal and craving in female CUD patients only,<sup>10-12,30</sup> sex-dependent differences in WM-related PFC activation can be expected as well.

The main aim of this study was to explore sex-dependent differences in WM-related PFC activation in a relatively large sample of regular CUs (27 males and 28 females) and non-cocaine users (non-CU: 26 males and 28 females) using a standardized WM paradigm (the n-back task<sup>31</sup>). It was hypothesized that (i) CUs would show higher WM-related (2-back > 0-back; 2-back > 1-back) PFC activation compared with non-CUs, (ii) females would show higher WM-related PFC activation compared with males, and (iii) WM-related PFC activation would be highest in female CUs, reflecting inefficient WM-related processes. Of note, because of the mixed and limited previous findings, the direction of these hypothesized effects is highly speculative.

## 2 | METHODS AND MATERIALS

### 2.1 | Participants

This study is part of a large project designed to investigate the role of sex in the neurocognitive mechanisms underlying CUD. Fifty-four regular CUs and 54 matched non-CUs who conducted the n-back functional magnetic resonance imaging (fMRI) task were included in this study. All participants were between 18 and 45 years of age and free from any MRI contraindications. CUs used cocaine (intranasally) at least four times a month in the past 6 months (CUs). Non-CUs were excluded if they smoked regularly (at least once per week), had an Alcohol Use Disorders Identification Test (AUDIT)<sup>32</sup> score > 12, used cocaine more than five times in their life, or used illicit substances more than five times in the past 6 months. 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).

### 2.2 | Assessment of substance use and psychological functioning

Severity of depressive symptoms was assessed using the Beck Depression Inventory (BDI-II<sup>33</sup>), state and trait anxiety was assessed using

the State and Trait Anxiety Inventory (STAI<sup>34</sup>), attention deficit hyperactive disorder (ADHD) symptom severity was measured using the ADHD Rating Scale (ADHD-RS<sup>35</sup>), and impulsivity was assessed with the Barratt Impulsiveness Scale (BIS-11<sup>36</sup>) in all participants. 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 (DUDIT<sup>37</sup>), cocaine use (grams and days per month) in the 28 days prior to study participation was assessed using the Time Line Follow-Back procedure,<sup>38</sup> and onset age of regular use was assessed using an in-house questionnaire. Moreover, motivation to change cocaine use was assessed using the Readiness to Change Questionnaire (RCQ<sup>39</sup>), smoking behavior (number of smoking days per week and cigarettes per day) was assessed using an in-house questionnaire, severity of cannabis use was assessed using the Cannabis Use Disorder Identification Test-Revised.<sup>40</sup> Current DSM-5 symptoms for CUD, and cannabis use disorder and AUD were assessed using a self-reported questionnaire based on the SCID.<sup>41</sup>

## 2.3 | Procedures

Participants were recruited through social media and local advertisements in the Amsterdam area, the Netherlands. After signing informed consent, participants were screened on inclusion and exclusion criteria. On the day of testing, participants first completed the questionnaires, after which the MRI scan was made. Participants were instructed to abstain from any drug use in the 24-h preceding the MRI scan.

## 2.4 | The n-back task

The n-back task<sup>22</sup> consisted of alternating blocks with three load levels: 0-back, 1-back, and 2-back. During each block, participants viewed a series of 15 letters in sequence, including five targets. Blocks lasted 30 s (each stimulus lasted 2 s), and the interblock interval was 5 s, during which the block instructions were repeated. In 0-back blocks, participants were instructed to indicate when the target letter “X” appeared on the screen. In 1-back blocks, participants had to decide if the letter on the screen was identical to the previous one. In 2-back blocks, targets were those letters identical to the letter presented two trials back. Participants were instructed to press a right response box button for targets (right index finger) and a left button for nontargets (left index finger). No additional speed or accuracy instructions were given. Each load level was repeated four times resulting in a 7-min task of 12 blocks. Prior to scanning, all participants first completed a practice block of the n-back task outside of the scanner.

## 2.5 | fMRI acquisition and preprocessing

A 3.0-Tesla Philips Achieva scanner (Philips Medical Systems, Best, the Netherlands) with a 32-channel head coil was used for data

acquisition. A T1-3D anatomical scan was acquired (TR/TE 8.2/3.8; matrix 240 × 240; 1 × 1 × 1 mm<sup>3</sup> voxel; transversal slices, 8° flip angle) for anatomical reference. Echo planar images (EPIs) were recorded during the n-back task, with 36 ascending axial slices (1 × 1 × 1 mm<sup>3</sup> voxel size; slice gap 3 mm; TR/TE 1.999/28 ms; matrix 80 × 80, 80° flip angle).

Data were preprocessed using fMRIPrep 1.3.2<sup>42</sup>: the anatomical scans were corrected for intensity nonuniformity, skull-stripped, spatially normalized, and segmented into cerebrospinal fluid, white matter, and gray matter. The functional data were corrected for susceptibility distortions using a deformation field and subsequently coregistered, motion corrected, and smoothed. ICA-AROMA<sup>43</sup> was used to automatically remove motion artifacts, and data were resampled to standard space. Further details on the pre-processing pipeline can be found in the Supporting Information.

fMRI data were further analyzed using SPM12 (<http://www.fil.ion.ucl.ac.uk/spm>). First level models included separate regressors for the 0-back, 1-back, and 2-back blocks. These regressors were 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 contrasts for the 0-back, 1-back, and 2-back blocks were subsequently entered in a second level model to test for the main and interaction effects of sex, group, and n-back load.

## 2.6 | Statistical analyses

Demographics, scores on (clinical) questionnaires, and n-back behavioral performance were compared between groups with standard univariate analysis of variance (ANOVA) in SPSS for Windows (v.26.0). Differences between groups and sexes in age, alcohol use severity (AUDIT), depressive symptoms (BDI), state and trait anxiety (STAI), impulsivity (BIS-11), and ADHD symptom severity (ADHD-RS) were assessed using 2 × 2 ANOVAs, testing both main and interaction effects. One-way ANOVAs were subsequently used to test sex differences within the CU group in cocaine use (grams per month and days per month), cocaine use severity (DUDIT), onset age of regular cocaine use, and cannabis use severity (CUDIT). Chi-square tests were additionally used to test for sex differences in the severity of cocaine, alcohol, and cannabis use disorder (mild, moderate, or severe according to the DSM-5 criteria), the prevalence of smoking (percent weekly smokers and percent daily smokers), and motivation to change cocaine use. Sex and group differences in n-back performance were assessed in terms of mean reaction time of correct responses and accuracy (proportion correct), using repeated measures ANOVAs.

To test for main and interaction effects of group, sex, and n-back load (2-back > 0-back and 2-back > 1-back), a whole-brain analysis was performed, with mean framewise displacement (FD) values for each subject as covariate of noninterest to account for potential motion effect. Whole brain analyses were family-wise error (FWE) rate corrected on cluster level ( $p < 0.05$ ), with an initial height threshold on the voxel level of  $p < 0.001$ . This analysis was repeated to test whether

significant effects were still present after correcting for potential confounding variables. Variables were treated as confounders when there was a significant interaction effect between group and sex on these variables. This was tested for age, education, AUDIT, BDI, ADHD-RS, STAI, and BIS. When a significant whole brain interaction effect was found, the nature of this interaction was explored by performing pairwise comparisons (between sexes within groups and between groups within sexes) using a small volume correction where the mask of the significant cluster served as the small volume. Additionally, the Marsbar toolbox (<http://marsbar.sourceforge.net>) was used to extract the mean activity of the significant cluster(s) visualization purposes.

A second whole brain analysis was performed within the CU group only, with cocaine use (grams per month), cocaine use severity (DUDIT-scores), as well as its interaction with sex as regressors of interest, correcting for variations in FD, to test whether cocaine use and cocaine use severity were associated with WM-related (2-back > 0-back; 2-back > 1-back) brain activity in a sex-dependent manner. This analysis was repeated to test whether significant effects were still present after correcting for potential confounding variables.

### 3 | RESULTS

#### 3.1 | Demographic and clinical characteristics

On average, male and female CUs started using cocaine regularly at the age of 23.5 and 21.4 and used 5.5 and 3.8 g of cocaine per month, on 7.4 and 4.9 days, respectively. Most CUs met the DSM-5 criteria for CUD (males: 85%, females: 89%). Based on the RCQ, the majority of CUs was actively trying to change cocaine intake (males: 59%, females: 63%), although only 3% of the participants reported to have (had) professional help for reducing their cocaine use. Two thirds of all CUs met the DSM-5 criteria for AUD (males: 85%, females: 59%), whereas less than one third of the CUs met the DSM-5 criteria for cannabis use disorder (males: 30%, females: 15%). There were no sex differences in the amount of cocaine used per month, readiness to change cocaine use, tobacco use, the prevalence of a DSM-5 diagnosis for CUD, cannabis use disorder or AUD, cocaine use severity (DUDIT), alcohol use severity (AUDIT), or cannabis use severity (CUDIT-R). The only significant sex difference was that CU females reported to use cocaine on fewer days per month compared with CU males. Therefore, days of cocaine use per month was treated as a confounder in an exploratory within-group fMRI analysis. See Table 1 for detailed substance use characteristics and statistics.

CUs and non-CUs had similar age, educational level, and trait anxiety scores, but CUs had significantly higher AUDIT, state anxiety, impulsivity (BIS attention and BIS planning), and ADHD-RS (childhood and past 6 month) scores. Additionally, females had significant higher state anxiety scores compared with males, whereas males reported higher childhood ADHD-RS than females. There was a significant group by sex interaction effect on depressive symptoms (BDI scores), impulsivity (BIS total and motor subscale), and ADHD-RS scores in the past 6 months. Follow-up tests revealed that although both male CUs

and female CUs scored higher on these variables compared with non-CU male and non-CU females, female CUs had significant higher BDI, BIS total and BIS motor scores compared with male CUs, while no such sex differences were present within non-CUs. Because of these differences, BDI, BIS motor, BIS total, and adult ADHD-RS scores were treated as confounders in the fMRI analyses. See Table 2 for all values and statistics.

#### 3.2 | Behavioral results n-back task

There were no significant differences between groups or sexes in n-back performance. There was a significant main effect of n-back load ( $F_{2,202} = 182.11, p < 0.001$ ) on reaction times, with reaction times increasing with increasing n-back load. The other main or interaction effects were not significant. There was a significant main effect of n-back load ( $F_{2,204} = 103.47, p < 0.001$ ) on accuracy, with accuracy decreasing with increasing n-back load. The other main and interaction effects were nonsignificant. See Figure 1. See the Supporting Information for a sensitivity analysis on how large the effect size needs to be to demonstrate significant main and interaction effects of group and sex.

#### 3.3 | fMRI results n-back task

##### 3.3.1 | Main task effect

The main task effects were as expected, with strong WM-related (2-back > 0-back and 2-back > 1-back) activation of fronto-parietal areas and deactivation of the default mode network (Figure 2 and Table S1).

##### 3.3.2 | WM-load, group and sex interaction effects

WM-related brain activation (2-back > 0-back or 2-back > 1-back) did not differ between groups or sexes. For the 2-back > 0-back contrast, there was a significant group by sex interaction in the left dorsal MFG (dMFG). See Table 3 and Figure 2. Pairwise comparisons on this specific cluster demonstrated that the non-CU males had higher WM-related activation in this region than non-CU females ( $p_{FWE-corrected \text{ on peak level}} = 0.002$ ), although no such difference was between CU males and females. In addition, within non-CU males displayed higher WM-related activation in this region compared to CU males ( $p_{FWE-corrected \text{ on peak level}} = 0.006$ ), whereas CU females displayed higher activation in this region compared to non-CU females ( $p_{FWE-corrected \text{ on peak level}} = 0.002$ ). Adding BDI, BIS-total, BIS-motor, and ADHD symptom severity scores as regressors of noninterest in the whole brain analysis did not alter the outcomes of these analyses (results not reported). There was no significant group by sex interaction effect for the 2-back > 1-back contrast.

An exploratory regression analysis was performed to assess the relationship between WM-related (2-back > 0-back) dMFG activation

**TABLE 1** Substance use characteristics in male and female cocaine users

	Cocaine users		Main effect sex
	Men (n = 27)	Women (n = 27)	
Cocaine use			
Onset age regular use	23.5 (5.3)	21.4 (4.4)	$F_{1,50} = 2.4, p = 0.12$
Grams per month <sup>a, b</sup>	5.5 (4.1)	3.8 (3.8)	$F_{1,52} = 2.61, p = 0.11$
Days per month <sup>a, b</sup>	7.4 (4.7)	4.9 (3.3)	$F_{1,52} = 5.3, p = 0.03$
Cocaine use disorder (DSM-5)			
			$\chi^2 = 1.43, p = 0.70$
% no cocaine use disorder	15% (n = 4)	11% (n = 3)	
% mild cocaine use disorder	26% (n = 7)	15% (n = 4)	
% moderate cocaine use disorder	22% (n = 6)	26% (n = 7)	
% severe cocaine use disorder	37% (n = 10)	48% (n = 13)	
Cocaine use severity (DUDIT) <sup>a</sup>	16.7 (6.0)	16.3 (4.7)	$F_{1,52} = 0.08, p = 0.78$
Readiness to change (RCQ)			
			$\chi^2 = 0.48, p = 0.79$
Precontemplation	26% (n = 7)	19% (n = 5)	
Contemplation	15% (n = 4)	19% (n = 5)	
Action	59% (n = 16)	63% (n = 17)	
Tobacco use			
Percent weekly smokers	52% (n = 14)	74% (n = 20)	$\chi^2 = 2.86, p = 0.09$
Percent daily smokers	30% (n = 8)	33% (n = 8)	$\chi^2 = 0.09, p = 0.77$
Alcohol use disorder (DSM-5)			
			$\chi^2 = 1.94, p = 0.58$
% no alcohol use disorder	15% (n = 4)	41% (n = 11)	
% mild alcohol use disorder	22% (n = 6)	26% (n = 7)	
% moderate alcohol use disorder	26% (n = 7)	11% (n = 3)	
% severe alcohol use disorder	37% (n = 10)	22% (n = 6)	
Cannabis use disorder (DSM-5)			
			$\chi^2 = 3.51, p = 0.32$
% no cannabis use disorder	70% (n = 19)	85% (n = 23)	
% mild cannabis use disorder	15% (n = 4)	4% (n = 1)	
% moderate cannabis use disorder	11% (n = 3)	4% (n = 1)	
% severe cannabis use disorder	4% (n = 1)	7% (n = 2)	
Cannabis use severity (CUDIT) <sup>a</sup>	5.9 (7.7)	4.8 (7.6)	$F_{1,52} = 0.25, p = 0.62$

Abbreviations: CUDIT, Cannabis Use Disorder identification test; DUDIT, Drug Use Disorder Identification Test; RCQ, Readiness to Change Questionnaire.

<sup>a</sup>Means (standard deviations) or % (n) are depicted.

<sup>b</sup>TLFB data of n = 8 subjects were missing (four women and three men). Cocaine using data were based on information provided during screening.

and cocaine use severity, grams of cocaine use per month, and days of cocaine use per month in the CU group only. This analysis (with FD and sex included as covariates) demonstrated that none of these variables were significantly associated with WM-related dMFG activation (DUDIT:  $B = -0.15, t = -0.97, p = 0.34$ ; days/month:  $B = -0.46, t = -1.99, p = 0.051$ ; grams/month:  $B = -0.04, t = -0.26, p = 0.80$ ).

### 3.3.3 | Within CU group whole brain regression analyses

Whole brain regression analyses with cocaine use (grams of cocaine per month) and cocaine use severity (DUDIT scores) in the CU group demonstrated that cocaine use was negatively associated with WM-

related activation of the vermis (2-back > 0-back) and right calcarine sulcus/bilateral cuneus (2-back > 0-back and 2-back > 1-back). Cocaine use was positively associated with WM-related activation of the left cerebellum (2-back > 0-back and 2-back > 1-back) and lingual gyrus and vermis (2-back > 1-back). The association between cocaine use and WM-related activation of the cerebellum, vermis, and occipital cortex was significantly moderated by sex: the association was positive in males but negative in females. In addition, although cocaine use was not associated with any WM-related brain activation, the association between cocaine use severity and WM-related (2-back > 1-back) activation in the left insula, inferior frontal gyrus, the cerebellum, and vermis was also moderated by sex, with a negative association in females, but not in males. Adding days of cocaine use per month as confounder to the model did not change the outcome of these results. See Table 4 and Figure 3.

**TABLE 2** Demographic and clinical variables: Main and interaction effects of group and sex

	Nondrug using controls		Cocaine users		Main effect sex	Main effect group	Sex * Group interaction effect
	Men (n = 26)	Women (n = 28)	Men (n = 27)	Women (n = 27)			
Age <sup>a</sup>	26.0 (5.7)	26.3 (5.0)	28.5 (6.5)	26.4 (56.8)	$F_{1,104} = 0.86$ , $p = 0.36$	$F_{1,104} = 0.97$ , $p = 0.33$	$F_{1,104} = 0.89$ , $p = 0.35$
Education <sup>b</sup>					$\chi^2 = 2.3$ , $p = 0.51$	$\chi^2 = 5.9$ , $p = 0.12$	
Elementary school (prevocational) secondary	0%	0%	0	4%			
Senior general/preuniversity	8%	7%	30%	15%			
Higher professional/university	34%	29%	18%	33%			
Alcohol use severity (AUDIT) <sup>a</sup>	3.8 (3.1)	4.5 (3.0)	10.8 (5.9)	12.2 (3.9)	$F_{1,104} = 1.8$ , $p = 0.19$	$F_{1,104} = 84.27$ , $p < 0.001$	$F_{1,104} = 0.14$ , $p = 0.71$
Depressive symptoms (BDI) <sup>a</sup>	4.7 (3.7)	4.5 (5.2)	9.0 (9.0)	14.6 (8.2)	$F_{1,104} = 4.12$ , $p < 0.05$	$F_{1,104} = 29.31$ , $p < 0.001$	$F_{1,104} = 6.61$ , $p = 0.03$
ADHD severity (ADHD-RS)							
Childhood	21.0 (16.3)	12.9 (13.5)	28.1 (15.3)	22.9 (17.1)	$F_{1,104} = 4.9$ , $p = 0.029$	$F_{1,104} = 8.1$ , $p = 0.005$	$F_{1,104} = 0.2$ , $p = 0.6$
Past 6 months	15.2 (8.2)	13.4 (8.0)	20.8 (11.3)	27.3 (13.6)	$F_{1,104} = 1.3$ , $p = 0.25$	$F_{1,104} = 23.1$ , $p < 0.001$	$F_{1,104} = 4.2$ , $p = 0.04$
Anxiety (STAI) <sup>a</sup>							
Trait <sup>a</sup>	30.9 (7.7)	30.9 (6.3)	32.8 (8.7)	34.1 (7.4)	$F_{1,104} = 0.19$ , $p = 0.66$	$F_{1,104} = 3.2$ , $p = 0.08$	$F_{1,104} = 0.23$ , $p = 0.63$
State <sup>a</sup>	34.0 (8.6)	35.1 (8.6)	35.6 (11.1)	41.1 (9.7)	$F_{1,104} = 4.02$ , $p < 0.05$	$F_{1,104} = 5.23$ , $p = 0.03$	$F_{1,104} = 2.08$ , $p = 0.15$
Impulsivity (BIS) <sup>a</sup>							
Total <sup>a</sup>	55.5 (8.4)	55.5 (8.6)	63.9 (10.9)	71.8 (12.3)	$F_{1,104} = 4.00$ , $p < 0.05$	$F_{1,104} = 39.6$ , $p < 0.001$	$F_{1,104} = 4.2$ , $p = 0.04$ <sup>**</sup>
Motor <sup>a</sup>	20.4 (2.6)	19.9 (3.3)	23.2 (4.5)	26.5 (5.2)	$F_{1,104} = 3.18$ , $p = 0.08$	$F_{1,104} = 36.8$ , $p < 0.001$	$F_{1,104} = 6.32$ , $p = 0.01$ <sup>***</sup>
Attention <sup>a</sup>	14.7 (3.6)	14.6 (3.0)	16.0 (4.5)	18.8 (4.6)	$F_{1,104} = 3.3$ , $p = 0.07$	$F_{1,104} = 12.6$ , $p = 0.001$	$F_{1,104} = 3.6$ , $p = 0.06$
Planning <sup>a</sup>	20.4 (4.4)	21.0 (4.4)	24.7 (4.1)	26.5 (4.8)	$F_{1,104} = 1.8$ , $p = 0.08$	$F_{1,104} = 33.4$ , $p < 0.001$	$F_{1,104} = 0.50$ , $p = 0.48$
Framewise displacement (mm)	0.12 (0.05)	0.11 (0.05)	0.18 (0.13)	0.15 (0.06)	$F_{1,104} = 1.8$ , $p = 0.18$	$F_{1,104} = 10.2$ , $p = 0.002$	$F_{1,104} = 0.69$ , $p = 0.41$

Abbreviations: ADHD-RS, Attention Deficit Hyperactive Disorder Rating Scale; AUDIT, Alcohol Use Disorder Identification Test; BDI, Beck Depression Inventory; BIS, Barrat Impulsiveness Scale; STAI: State and Trait Anxiety Inventory.

<sup>a</sup>Means (standard deviation) or % (n) are depicted.

<sup>b</sup>Highest finished educational level.

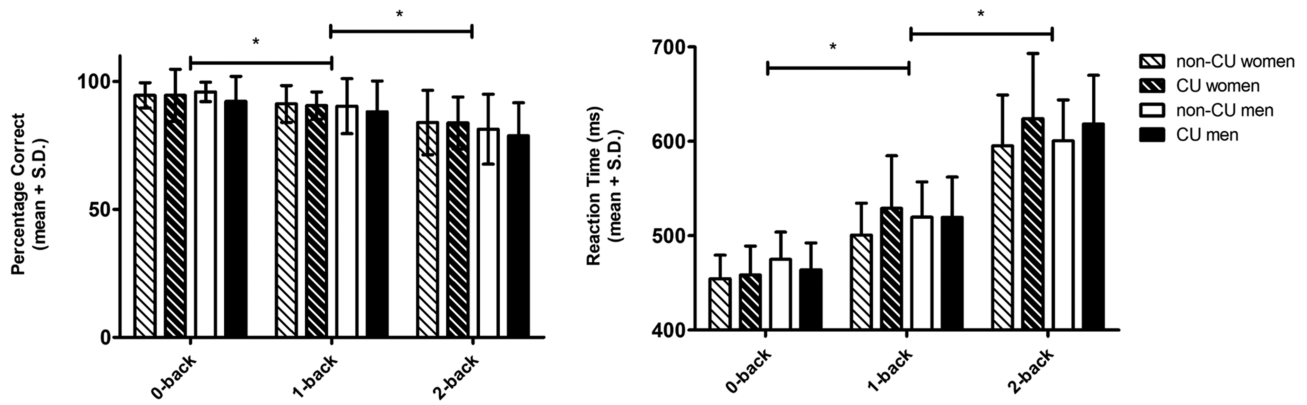
\*Follow-up tests BDI-scores: CU women > CU men ( $F_{1,52} = 5.59$ ,  $p = 0.02$ ); Non-CU women = non-CU men ( $F_{1,52} = 0.02$ ,  $p = 0.90$ ); CU women > non-CU women ( $F_{1,53} = 29.59$ ,  $p < 0.001$ ); CU men > non-CU men ( $F_{1,51} = 5.16$ ,  $p = 0.03$ ). \*\*Follow-up tests BIS total: CU women > CU men ( $F_{1,52} = 6.24$ ,  $p = 0.02$ ); Non-CU women = non-CU men ( $F_{1,52} = 0.01$ ,  $p = 0.98$ ); CU women > non-CU women ( $F_{1,53} = 32.71$ ,  $p < 0.001$ ); CU men > non-CU men ( $F_{1,51} = 9.69$ ,  $p = 0.003$ ). \*\*\*Follow-up tests BIS motor: CU women > CU men ( $F_{1,52} = 6.34$ ,  $p = 0.015$ ); Non-CU women = non-CU men ( $F_{1,52} = 0.49$ ,  $p = 0.49$ ); CU women > non-CU women ( $F_{1,53} = 32.45$ ,  $p < 0.001$ ); CU men > non-CU men ( $F_{1,51} = 7.44$ ,  $p = 0.01$ ).

## 4 | DISCUSSION

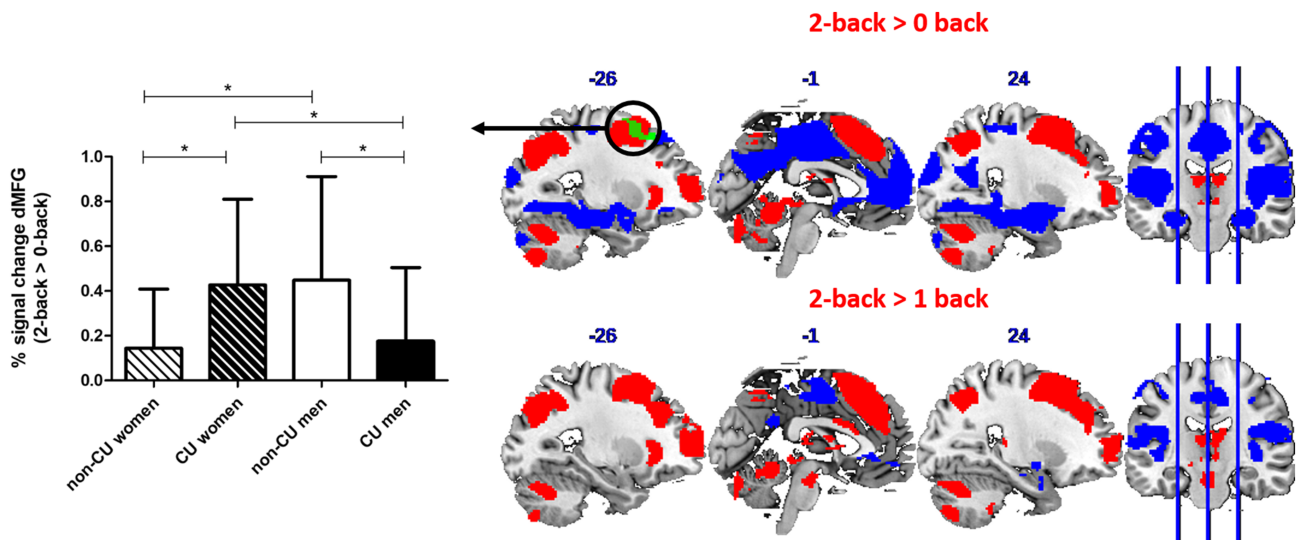
Women have been structurally ignored in addiction-related (neuroimaging) research, and therefore, little is known about sex differences in

the neuropathology of addiction. The aim of this explorative study was to investigate sex differences in WM-related PFC functioning in regular CUs, as deficits in PFC-mediated cognitive control are crucially involved in the transition from recreational to compulsive cocaine





**FIGURE 1** Main and interaction effects of working memory (WM) load, group, and sex on reaction time and percentage correct during the n-back task. Although there was a main effect of WM-load on reaction time (increase) and percentage correct (decrease), these effects were not moderated by sex, group, or both. CU, cocaine user; WM, working memory



**FIGURE 2** Main and interaction effects of WM load, group and sex. In red, brain regions activated with increasing WM load. In blue, brain regions deactivated with increasing WM-load. In green, group differences in WM-related brain activation that are significantly moderated by sex. Mean activity of the whole cluster is extracted and plotted for visualization purposes. The error bars represent the 90% confidence interval. CU, cocaine user; WM, working memory

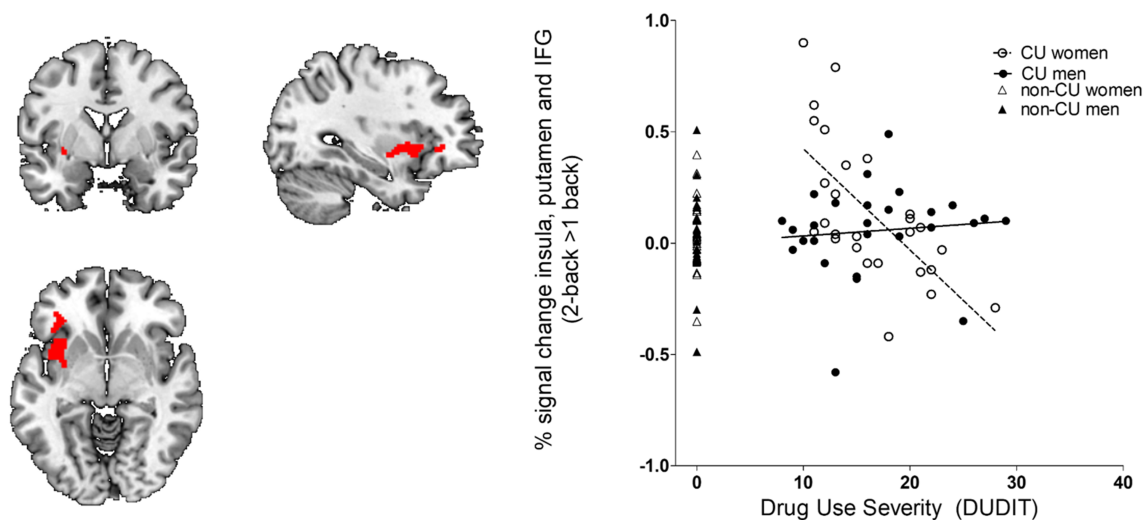
**TABLE 3** Main and interaction effects of group and sex on working memory-related whole brain activation

	Cluster size (n voxels)	Cluster p-value FWE-corrected	Peak voxel z-value	Peak voxel MNI coordinates (x, y, z)			Voxel region
Main effect group or sex	No significant voxels						
Group x sex interaction							
2-back > 0-back	218	0.016	4.26	-24	8	60	Left (dorsal) middle frontal gyrus

Note: All 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  $p < 0.001$ .

use.<sup>5</sup> WM-related (2-back > 0-back; 2-back > 1-back) PFC activity was hypothesized to be higher in CUs compared with non-CUs, with larger differences in female compare with male CUs. There was no main effect of group or sex on brain activity or behavior; however, we did observe a significant group by sex interaction effect in WM-

related (2-back > 0-back) left dMFG activation: CU females displayed higher dMFG activity compared with non-CU females, whereas CU males displayed lower dMFG activity compared with non-CU males. Furthermore, WM-related activation of the vIPFC (including the inferior frontal gyrus, insula, and putamen) was negatively associated with



**FIGURE 3** Working memory load-related activation (2-back > 1-back) of the insula, putamen, and inferior frontal gyrus (in red) is negatively associated with drug use severity in cocaine using women but not in cocaine using men. Nonetheless, the brain activation patterns are in the similar range as non-cocaine using controls. Mean activity of the whole cluster is extracted and plotted for visualization purposes. The error bars represent the 90% confidence interval. CU, cocaine user

cocaine use severity in female CUs, but not in males. Heightened WM-related PFC activation is suggested to reflect compensatory but inefficient information processing, leading to WM deficits.<sup>15</sup> As such, the current data support our hypothesis that PFC deficits are more strongly implicated in the neuropathology of CUD in females compared with males. Importantly, these findings highlight an urgent need to further unravel the role of sex in the mechanisms underlying CUD.

Although heightened WM-related PFC activation in CUD (compared with a control group) may reflect compensatory (but inefficient) mechanisms,<sup>15,18</sup> heightened PFC activation in recreative CUs (in the absence of behavioral deficits) has also been suggested to reflect resilience to stimulant dependence. In line with this, heightened WM-related activation of the ventrolateral and ventromedial PFC has been shown to protect against relapse in alcohol dependent patients.<sup>15</sup> In the current study, inferior frontal gyrus activity was negatively associated with cocaine use severity in female CUs only, perhaps reflecting sex-dependent resilience against the development of compulsive cocaine use. It should be noted, though, that the majority of CUs included in our study already transitioned from recreational to compulsive cocaine use. Alternatively, although WM-related dMFG activation was unrelated to cocaine use (severity), the negative association between cocaine use severity and WM-related ventrolateral PFC recruitment may reflect a sex-specific (neurotoxic) effect of cocaine use on the brain, supporting the hypothesis that females are more vulnerable to the (neurotoxic) effects of substances, including cocaine and alcohol.<sup>44</sup>

Unexpectedly, dMFG activation was higher in non-CU males compared with non-CU females. This is remarkable, as females generally display higher WM-related middle and medial PFC activity compared with males.<sup>28</sup> Interestingly, although various PFC regions are shown to be more active in females compared with males during

WM-related tasks,<sup>28</sup> there seems to be a sex-dependent effect on the lateralization of WM-related dMFG activity as well: higher WM-related activation of the *right* MFG was found in females compared with males, whereas higher WM-related activation of the *left* MFG was found in males,<sup>28</sup> which is in line with our finding in non-CUs. Sex differences in WM-related brain functioning and lateralization are suggested to result from a combination of prenatal hormonal (testosterone) exposure<sup>45</sup> and gender-related factors later in life.<sup>46</sup> Consequently, the current findings may be the result of neurodevelopmental differences, reflecting a sex-dependent predisposition to CUD rather than a consequence of cocaine use.

It is important to note that no significant group or sex differences were found in behavioral n-back performance. However, the n-back task is generally considered to be less reliable to assess behavioral WM-related deficits.<sup>47</sup> As such, the behavioral implications of the current findings remain speculative and future research may benefit from including a more reliable WM task outside the MRI scanner to assess behavioral WM performance.

Although the causal interplay between PFC functioning, CUD and sex can only be established with future longitudinal research, the current findings suggest that PFC deficits are more strongly implicated in the development, continuation, and perhaps also treatment of CUD in women. Because pharmacological enhancement of PFC control (using the noradrenergic  $\alpha 2$ -receptors agonist guanfacine)<sup>30</sup> reduced arousal and craving and improved cognitive control in women with a CUD specifically,<sup>10–12</sup> women with a CUD may benefit more from interventions targeted at improving PFC-related cognitive and emotional control processes.

Inconsistent results from previous SUD studies<sup>18–21,25,26</sup> may be explained by highly variable but mainly low numbers of female participants. An important strength of the current study is that it



was specifically set-up to elucidate sex differences in PFC functioning in regular CUs and non-CUs. As such, CU males and females were matched on most cocaine-use-related variables. Although we focused on including nontreatment seeking CUs, the majority of all included CUs met the DSM-5 criteria of CUD and were actively trying to change their cocaine use based on the readiness to change questionnaire. Therefore, the current findings likely generalize to treatment seeking CUs as well.

A limitation of the current study is that we only tested for sex differences without taking gender taking into account. According to the Sex and Gender Equity in Research (SAGER) guidelines, gender is an equally important determinant of health and well-being as sex.<sup>48</sup> Although the terms sex and gender are often confused in scientific literature, gender refers to the socially constructed roles, behaviors, 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. 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.<sup>49</sup> Moreover, CUD is generally associated with polysubstance use. Indeed, approximately two thirds of CUs met the DSM-5 criteria of an AUD and almost one third met the DMS-5 criteria of a cannabis use disorder. Although there were no sex differences in the prevalence of comorbid SUDs, we have previously demonstrated that deficits in PFC structure are strongly associated with the amount of polysubstance use across regular CUs.<sup>50</sup> Hence, we cannot fully exclude potential confounding effects of other substances on PFC functioning in the current study. In this study, we instructed CUs to remain abstinent for 24 h prior to study participation. We decided to 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,<sup>41</sup> which is much longer than its psychopharmacological effects. A urine test would, therefore, not have been a very accurate measure of intoxication in this specific population. 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.<sup>52</sup> Nonetheless, we cannot fully exclude the possibility that some CUs were (still) under the influence of some substances.

In conclusion, the current study provides important first evidence for sex-dependent differences in WM-related PFC recruitment among regular CUs. Although speculative, these data suggest that PFC deficits are more strongly implicated in the development, continuation, and possibly treatment of CUD in females compared with males. Most importantly, the current findings highlight the crucial need for (i) including both males and females in (pre)clinical addiction research and (ii) disaggregating (neuroimaging) findings for males and females separately.<sup>48</sup> Doing so will not only lead to a better understanding of (sex differences in) the (neuro)pathology of addiction but could also pave the way for the development of sex-tailored treatment of SUDs.

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## FINANCIAL DISCLOSURE

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## AUTHORS CONTRIBUTION

AMK was responsible for the study concept, design, data acquisition, analysis, and preparing the first draft of the manuscript. JC and RR 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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### SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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