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Enhanced Cue Reactivity to Cocaine Cues in Non-treatment Seeking Cocaine Smokers

Suchismita Ray[1*], Catherine Hanson[2] and Stephen José Hanson[2]

[1]*Center of Alcohol Studies, Rutgers, The State University of New Jersey, Piscataway, NJ 08854, USA*

[2]*Rutgers University Brain Imaging Center (RUBIC), Newark, NJ 07102, USA*

Abstract

Introduction: Cue reactivity is defined as an observable, classically conditioned response to drugs. Chronic cocaine use is associated with enhanced cue reactivity. Our aims were: (1) to evaluate reactivity to cocaine and neutral picture cues in non-treatment seeking chronic cocaine smokers who were abstinent from cocaine use for 72 hours and control participants using functional magnetic resonance imaging (fMRI), and (2) to assess whether cue reactivity related brain areas were correlated with subjective craving ratings.

Method: fMRI data were collected from non-treatment seeking cocaine-smokers (29-53 yrs.; 15M; 5F) who were abstinent from cocaine smoking for 72 hours, and control participants (25-53 yrs.; 13M; 4F) using a Siemens 3T magnet while they took part in a cue viewing task that included cocaine and neutral cues. Participants also provided craving ratings while they viewed the cues.

Results: Contrasting activation of cocaine smokers to that of controls revealed significantly greater activation in response to cocaine cues in the following brain areas: anterior cingulate gyrus, posterior cingulate gyrus, left insula, right amygdala, left precuneous, and bilateral orbitofrontal cortex, caudate, parahippocampal gyrus, thalamus, frontal pole, and lingual gyrus. In contrast, when comparing cocaine smokers to controls no significant difference in activation to neutral cues was observed. Increased cue reactivity was not positively correlated with cocaine users' subjective craving ratings.

Conclusion: Enhanced cue reactivity reflects cocaine users' increased salience to cocaine cues, and this enhancement may not indicate increased craving for the drug. Results have implications for treatment development. Future studies will examine how these cue reactivity related brain areas are causally related during viewing cocaine cues in cocaine users.

Keywords: Reactivity; Cocaine cues; Cue reactivity; Cocaine smokers

Introduction

Cue reactivity is defined as an observable, classically conditioned response to drugs and alcohol [1]. According to Kalivas and Volkow (2005) neuroadaptations as a result of chronic drug use are a major cause of drug addiction and compromise an addict's ability to inhibit drug seeking when he or she is exposed to cues that are associated with drug use. Thus, it is important to identify the brain regions involved in the dysfunctional decision to use cocaine upon cue exposure as this has promise to develop effective treatment for cocaine use disorder.

An abnormal functional organization in the brain of an individual with addictive disorder results in an enhanced salience of drug-related cues and weakened cognitive control [2]. According to the previous cue-elicited functional Magnetic Resonance Imaging (fMRI) and Positron Emission Tomography (PET) literature involving cocaine, cocaine cues activate the anterior cingulate cortex, dorsolateral prefrontal cortex, posterior cingulate cortex, amygdala, orbitofrontal cortex, thalamus, insula, dorsal striatum and ventral striatum in chronic users of cocaine [3-11].

In the previous cocaine cue reactivity studies, cocaine users were either receiving treatment [4,8,11], or were non-treatment seeking and abstaining from cocaine use ranging from two days [3,7] to two to 16 days [5,10] on the day of scan. It is conceivable that most of the participants in Bonson et al. and Grant et al. [3,7] studies and some of the participants in Duncan et al. and Wang et al. [5,10] studies had cocaine in their system on the day of their scan as only two days had elapsed since their last cocaine use. It is estimated that approximately 72 hours are required to allow for elimination of the active cocaine metabolites from one's system [12].

The aims of the present study were (1) to evaluate reactivity to cocaine and neutral picture cues in non-treatment seeking chronic cocaine smokers who were abstinent from cocaine use for 72 hours using fMRI, and (2) to assess whether cue reactivity related brain areas were correlated with subjective craving ratings. This study allowed us to examine brain areas activated in response to cocaine cues in chronic smokers of cocaine while they were not in significant acute cocaine withdrawal [13]. fMRI data were collected from non-treatment seeking cocaine smokers and similarly-aged healthy control participants with no cocaine experience while they performed a cue viewing task that presented cocaine and neutral picture cues. Subjective craving ratings were collected from the participants while they took part in the cue viewing task. We also examined whether activation in the cocaine cue processing brain areas was positively correlated with cocaine smokers' subjective craving ratings.

***Corresponding author:** Suchismita Ray, Assistant Research Professor, Center of Alcohol Studies, 607 Allison Road, Piscataway, NJ 08854, USA, Tel: 848-445-9391; Fax: 732-445-3500; E-mail: shmita@rci.rutgers.edu

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Method

Participants

Twenty (15M; 5F) non-treatment seeking chronic cocaine smokers abstinent from cocaine use for 72 hrs, and 17 (13M; 4F) age-, education-, and ethnic background matched healthy volunteers took part in the study (Table 1). The groups did not differ significantly in terms of age, education, alcohol use quantity, nicotine use frequency and quantity, and caffeine use frequency and quantity. Seven out of 20 cocaine smokers did not meet criteria for cocaine abuse or dependence. They were heavy users of cocaine. Since they were non-treatment-seeking, they did not report any distress from their use, which is critical to the diagnosis.

The main inclusion criteria for the study participants included English as first language, right handedness, near 20/20 vision (or corrected) and no report of childhood learning disability or special education. The main exclusion criteria for the study participants included serious medical conditions, a history of psychiatric or neurological disorder or treatment, lifetime diagnosis of any substance use disorder on the part of the prospective participant's biological mother (to rule out prenatal exposure effects), alcohol abuse and dependence including past dependence on alcohol, MRI contraindications, and for women, pregnancy.

Participants were included in the cocaine group if they had a history of smoked cocaine for at least two days per week for past six months (assessed by self-report), and had a current spending of at least $70 per week on cocaine. The primary current drug of choice for the cocaine group was cocaine and they did not meet a DSM-IV-R diagnosis of abuse or dependence for any other drugs, as confirmed by SCID [14]. The inclusion criteria for the control participants included no current or past drug use history and no alcohol abuse history on part of their first degree family members.

On the day of the study, all participants gave written informed consent and were administered a urine screen to rule out pregnancy in women, and to ensure negative urine toxicology for cocaine, methamphetamine, THC, opiate and benzodiazepines (One Step Multi-Drug Screen Test Panel). Their abstinence from alcohol was confirmed with a breathalyzer. At the end of the study, participants received a gift certificate worth $100 for their participation and were paid for their transportation.

Stimuli

Participants looked at 30 cocaine-related picture stimuli (15 stimuli presented twice) and 30 neutral picture stimuli (15 stimuli presented twice). Cocaine stimuli were supplied by Dr. Rita Goldstein of Icahn School of Medicine, Mount Sinai, and Dr. Robert Hester of The University of Melbourne. Additional stimuli were gathered from the Cognitive Neuroscience Laboratory at the Rutgers Center of Alcohol Studies. The cocaine stimuli included pictures of cocaine paraphernalia, and individuals smoking cocaine. The neutral stimuli which were nature scenes [4] were selected from non-copyrighted images on the internet.

Procedure

Cue viewing task

Participants viewed two blocks of cocaine cues and two blocks of neutral cues during the cue viewing task. The cocaine and neutral cue blocks were presented in a counterbalanced manner across participants. To give an example, if one participant viewed the blocks of cues in a particular sequence (cocaine, neutral, cocaine, neutral), the next participant viewed the blocks in a counterbalanced order (neutral, cocaine, neutral, cocaine). Participants viewed 15 visual stimuli in each block. Within the blocks stimuli were presented randomly and each stimulus was presented for 4 sec then followed by a fixation cross for 2 sec. The task was designed using E-prime (Psychology Software Tools, Inc., Pittsburgh, PA). To synchronize stimulus presentation with fMRI acquisition, a trigger pulse from the MRI console was used. All participants were administered a three item version of the cocaine craving questionnaire [15] after the presentation of the first neutral cue block and the first cocaine cue block. Exactly the same three items were used after the first neutral cue block and the first cocaine cue block. These items appeared one at a time for 10 sec. For example, an item ('I crave "coke" right now') appeared on the screen. Right below the item, a 7-point scale also appeared where 1 indicated 'strongly disagree' and 7 indicated 'strongly agree'. Participants were instructed to use the whole scale. Before the cue viewing task started, each participant was provided with a MRI compatible button-box with two buttons. Participants were instructed to place their index finger on the first button and to place their middle finger on the second button. They were instructed to use the first button with their index finger to indicate their craving responses. For example, if one participant's response was '7' for the item 'I crave "coke" right now', he needed to press the button for 7 times and this response was recorded in the E-prime data file for that participant. The cue viewing task took seven min to complete.

Image acquisition

Imaging data were obtained using a 3T Siemens Allegra head-only fMRI scanner equipped with a standard Siemens head coil. While participants performed the task, T2*-weighted echo planar images (functional images) were acquired (35 axial slices, voxel size 3×3×3 mm, interslice gap 1 mm, matrix size 64×64 mm, FOV=192 mm, TR=2000 ms, TE 25 ms, flip angle=90°) covering the entire brain. A sagittal T1-weighed structural scan (TR=1900 ms, TE=2.52 ms, matrix=256 × 256, FOV =256 mm, voxel size 1×1×1 mm, 176 1-mm slices with 0.5 mm gap) was made in order to co-register it with the fMRI data.

Image analysis

FSL 5.0.4 software was used for image preprocessing and data analysis.

(FMIRB's Software Library, www.fmirb.ox.ac.uk/fsl). Functional images were high-pass filtered; skull stripped using BET [16]; motion corrected using MCFLIRT [17]; and a Gaussian kernel of FWHM 6 mm was used to smooth the images. In order to model the cocaine cue and neutral cue blocks, a Gaussian hemodynamic response function and its temporal derivatives were applied to the basic waveform. BOLD scans for each participant were registered first to her or his anatomical scans, and then registered to standard space using the FSL's MNI (Montreal Neurologic Institute) template.

A two-level statistical analysis procedure was utilized. The first level analysis was aimed at brain activity related to picture cue type effect (cocaine cues vs. neutral cues) during the cue viewing task. At first level, two predictors were coded 'cocaine cues' and 'neutral cues' respectively, denoting mean brain activation during presentation of cocaine cues and neutral cues. Mean brain activation was analyzed by a GLM for each predictor in individual participants using FEAT (FMRI Expert Analysis Tool). The results were then put into a group (i.e., higher) level analysis using FLAME 1 mixed-effects [18]. In the

group-level whole brain analysis, average activation was determined for each group (cocaine users and controls) as well as the difference between the groups (cocaine users > controls contrast) for the total of 37 participants. Group level statistic images were thresholded using clusters determined by z>1.65 and a (corrected) cluster significance threshold of p=0.001 [19].

To assess whether activation in the cocaine cue processing brain areas was positively correlated with cocaine smokers' subjective craving ratings, correlations were computed between activation in the cocaine cue processing brain areas and craving ratings collected within the scanner.

Results

Craving results

For each participant, a craving score was calculated by averaging the three craving ratings [15]. Participants who could not provide any response were excluded from the analysis (n=11). Cocaine users compared to controls demonstrated a significantly enhanced craving rating to the cocaine cues, t (24)=2.81, p=0.01.

Cue reactivity

Contrasting activation of cocaine smokers to that of controls revealed significantly greater activation in response to cocaine cues in the following brain areas: anterior cingulate gyrus (Figure 1a), posterior cingulate gyrus (Figure 2a), left insula (Figure 3a), right amygdala (Figure 4a), bilateral orbitofrontal cortex (Figure 5a (right) and 6a (left)), left precuneous, and bilateral caudate, parahippocampal gyrus, thalamus, frontal pole, and lingual gyrus (Table 2). In contrast, when comparing cocaine smokers to controls no significant difference in activation to neutral cues was observed. Also, while control participants viewed cocaine cues, there was no activation in anterior cingulate gyrus, posterior cingulate gyrus, left insula, right amygdala, right orbitofrontal cortex, left orbitofrontal cortex (Figures 1b-6b) or in any other brain area.

Correlation analyses

Results showed that there was no significant positive correlation between the activation in the cocaine cue processing brain areas and craving ratings in chronic cocaine smokers.

Discussion

The purpose of the present study was two-fold. First, to evaluate reactivity to cocaine and neutral picture cues in non-treatment seeking chronic cocaine smokers who were abstinent from cocaine use for 72 hours using fMRI, and second, to assess whether activation in the cocaine cue processing brain areas was positively correlated with cocaine smokers' subjective craving ratings.

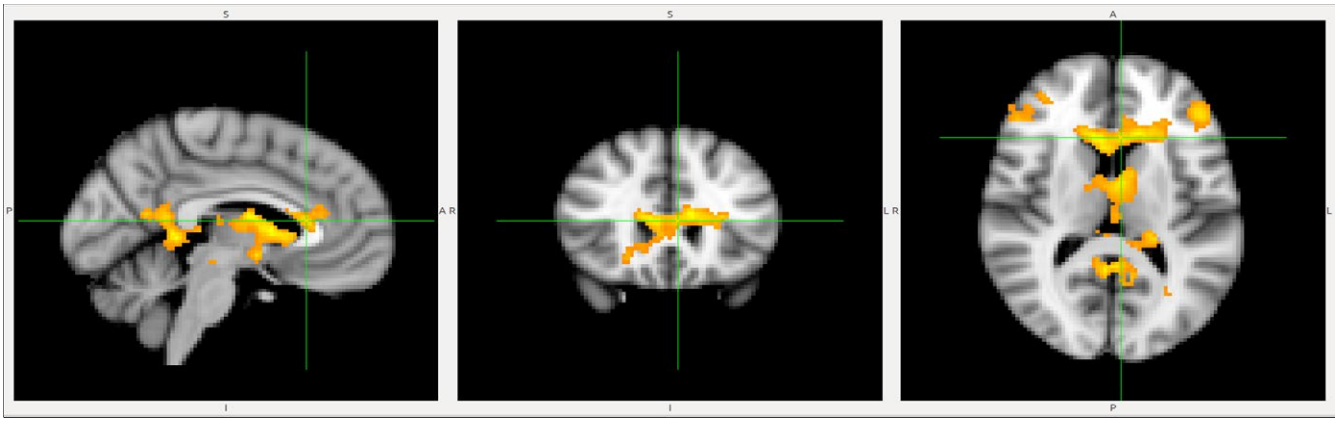

Figure 1a: Cocaine smokers compared to controls, showed increased activation in response to cocaine cues in anterior cingulate gyrus. Group-level *z* (Gaussianised *t*) statistic images were thresholded using clusters determined by z=1.65 and a (corrected) cluster significance threshold of p=0.001

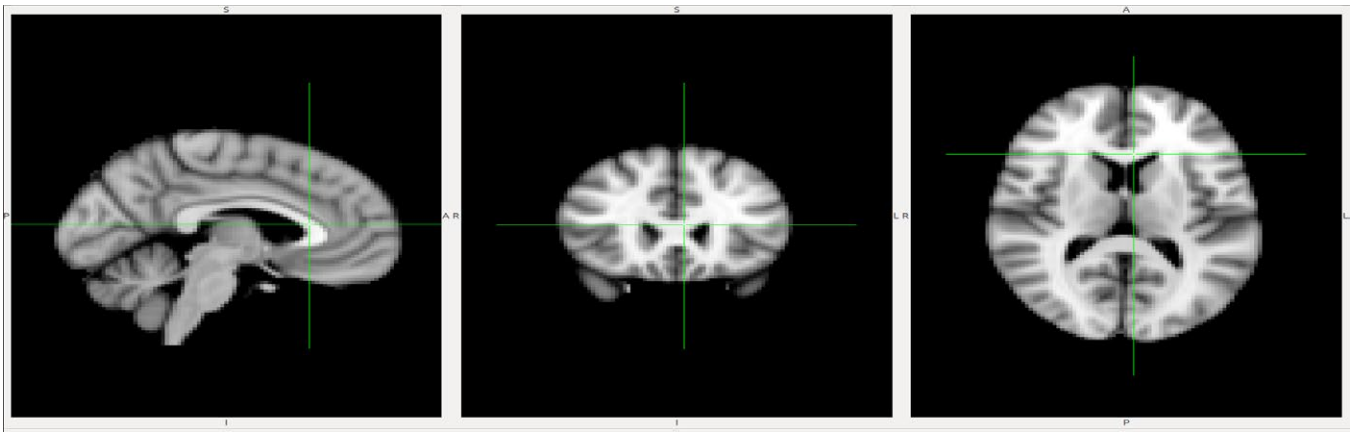

Figure 1b: Control participants' activation in anterior cingulate gyrus while they looked at cocaine cues.
*Group-level *z* (Gaussianised *t*) statistic images were thresholded using clusters determined by z=1.65 and a (corrected) cluster significance threshold of p=0.001

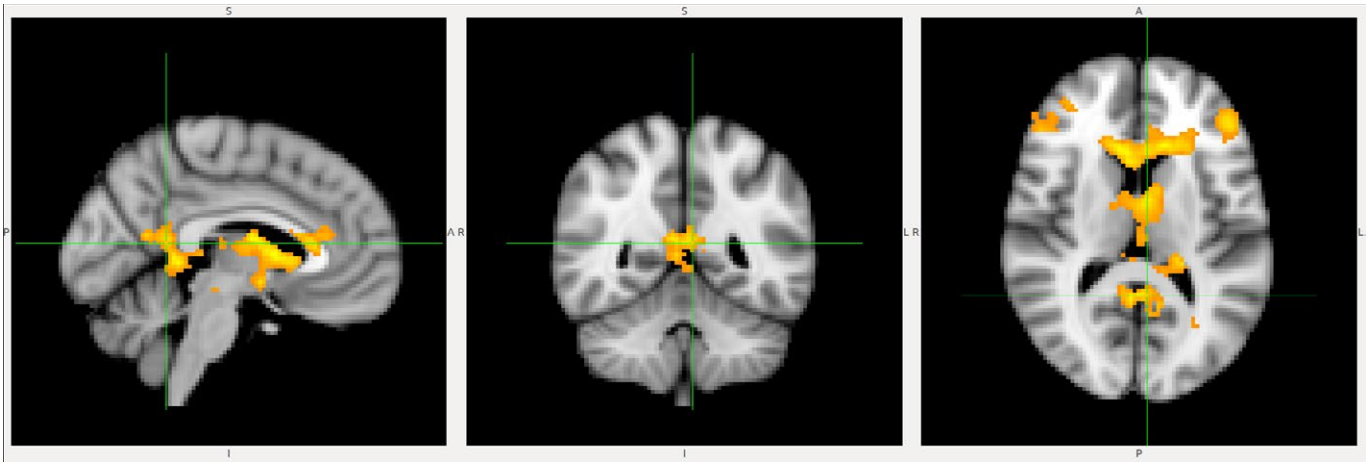

Figure 2a: Cocaine smokers compared to controls, showed increased activation in response to cocaine cues in posterior cingulate gyrus. Group-level *z* (Gaussianised *t*) statistic images were thresholded using clusters determined by z=1.65 and a (corrected) cluster significance threshold of p=0.001

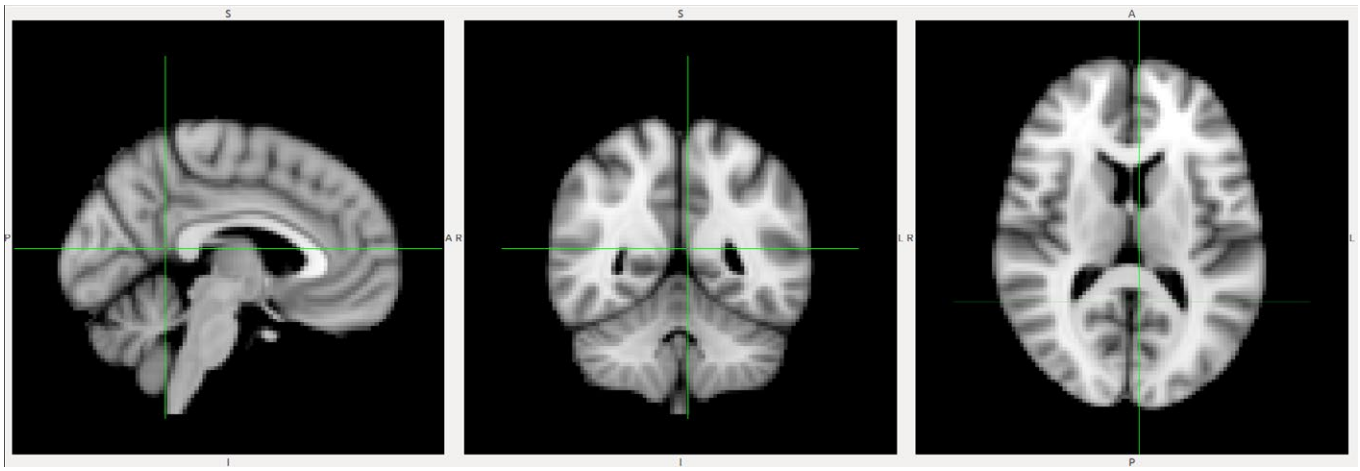

Figure 2b: Control participants' activation in posterior cingulate gyrus while they looked at cocaine cues.

*Group-level *z* (Gaussianised *t*) statistic images were thresholded using clusters determined by *z*=1.65 and a (corrected) cluster significance threshold of *p*=0.001

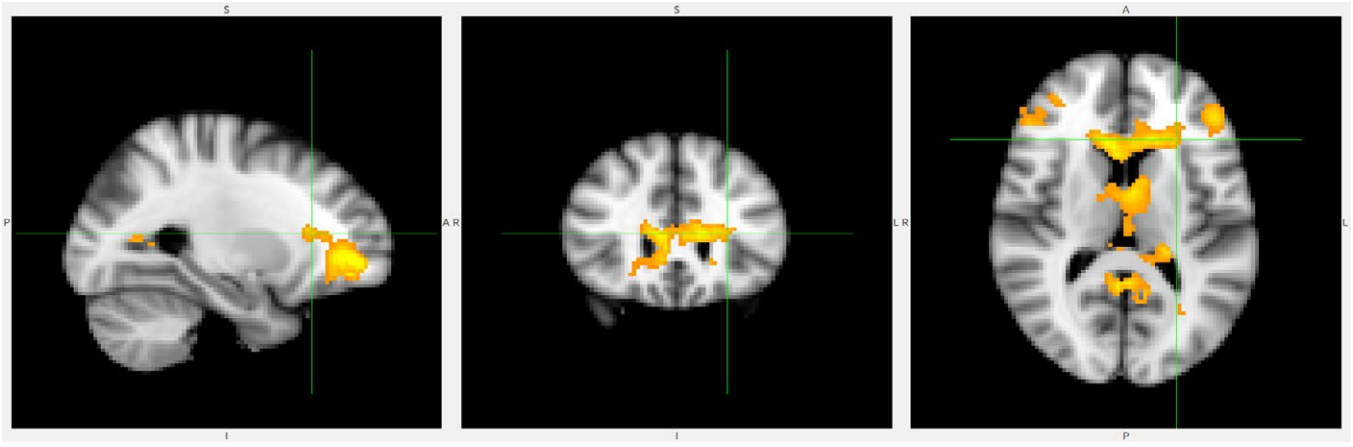

Figure 3a: Cocaine smokers compared to controls, showed increased activation in response to cocaine cues in left insula. Group-level *z* (Gaussianised *t*) statistic images were thresholded using clusters determined by *z*=1.65 and a (corrected) cluster significance threshold of *p*=0.001

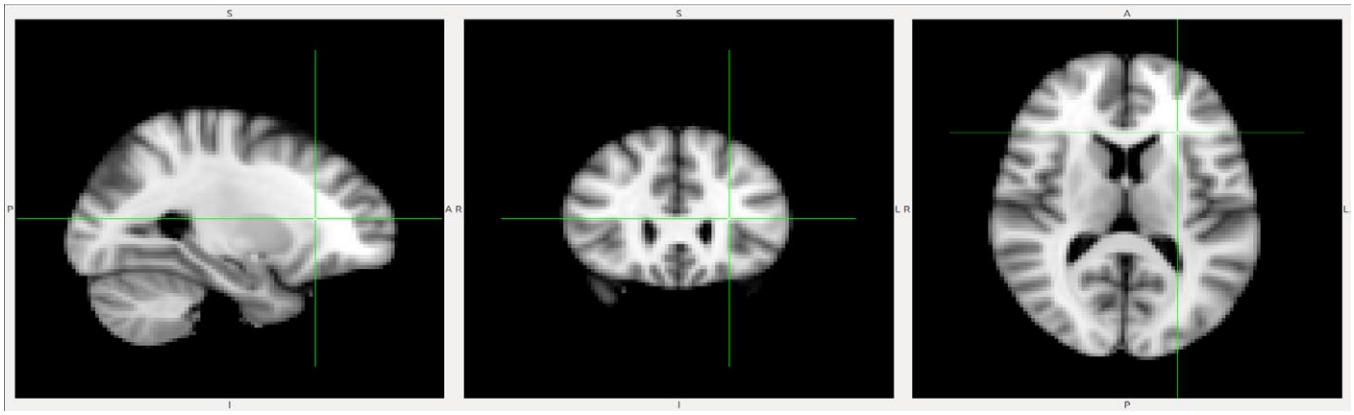

Figure 3b: Control participants' activation in left insula while they looked at cocaine cues.

*Group-level *z* (Gaussianised *t*) statistic images were thresholded using clusters determined by z=1.65 and a (corrected) cluster significance threshold of p=0.001

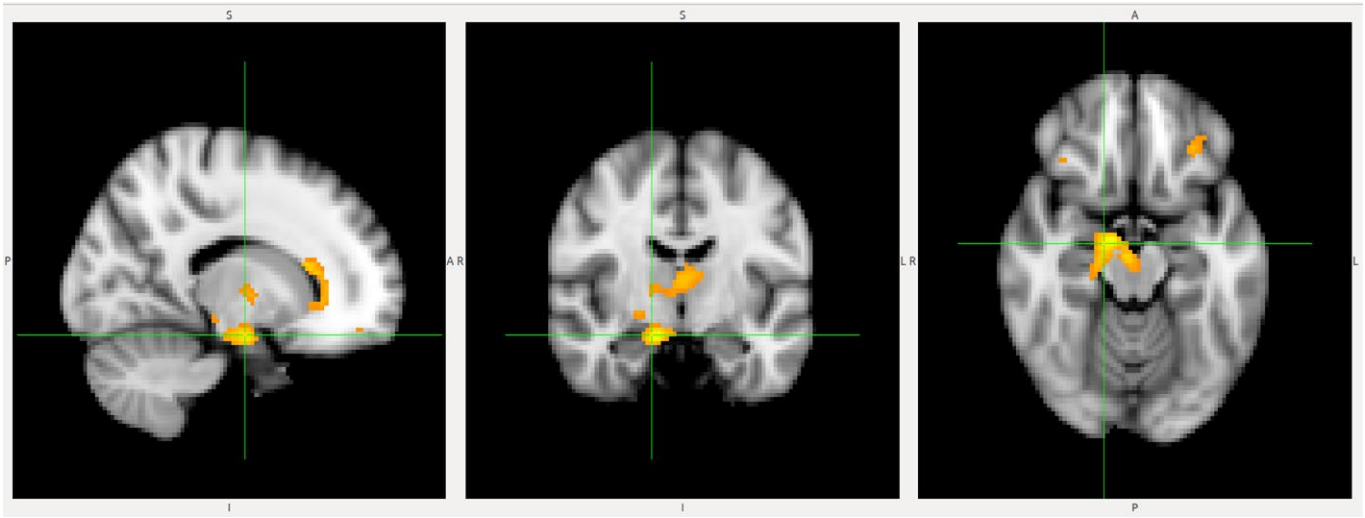

Figure 4a: Cocaine smokers compared to controls, showed increased activation in response to cocaine cues in right amygdala. Group-level *z* (Gaussianised *t*) statistic images were thresholded using clusters determined by *z* = 1.65 and a (corrected) cluster significance threshold of p=0.001

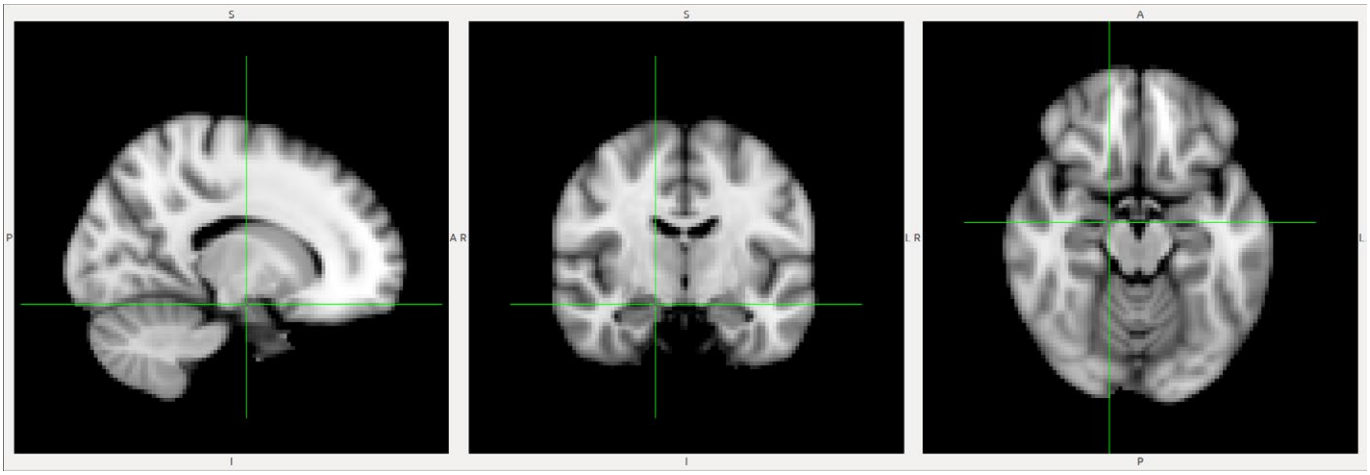

Figure 4b: Control participants' activation in right amygdala while they looked at cocaine cues.

*Group-level *z* (Gaussianised *t*) statistic images were thresholded using clusters determined by z=1.65 and a (corrected) cluster significance threshold of p=0.001

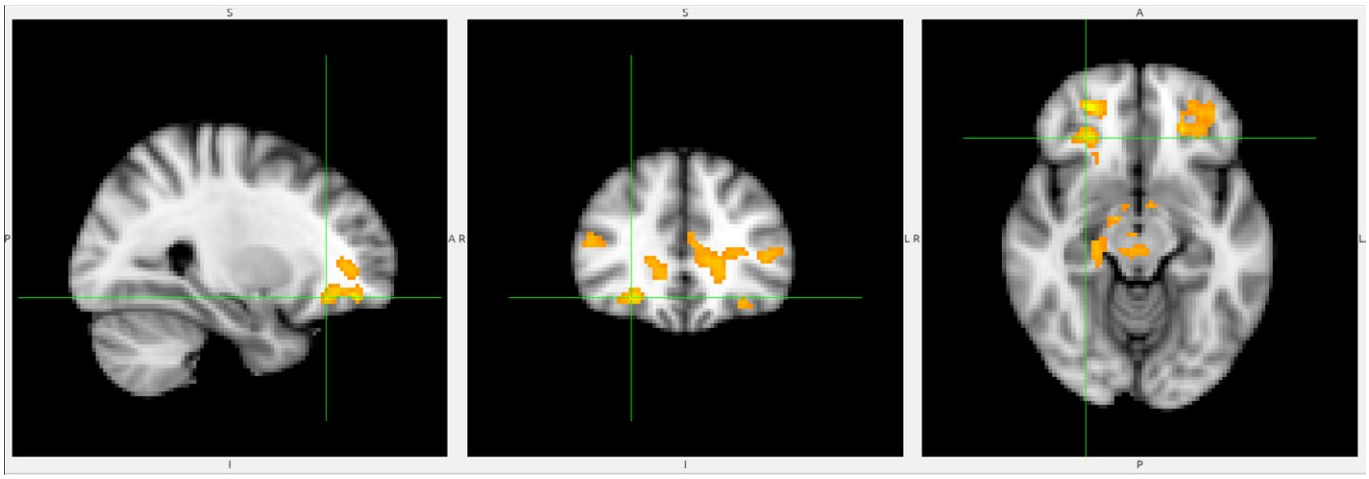

Figure 5a: Cocaine smokers compared to controls, showed increased activation in response to cocaine cues in right orbitofrontal cortex. Group-level *z* (Gaussianised *t*) statistic images were thresholded using clusters determined by z=1.65 and a (corrected) cluster significance threshold of p=0.001

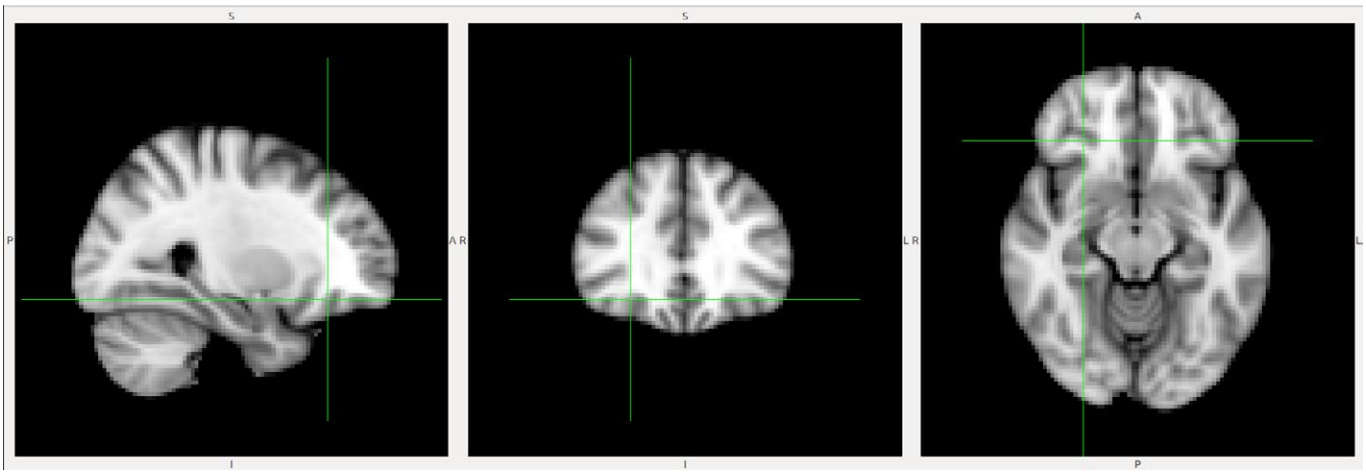

Figure 5b: Control participants' activation in right orbitofrontal cortex while they looked at cocaine cues.

*Group-level *z* (Gaussianised *t*) statistic images were thresholded using clusters determined by z=1.65 and a (corrected) cluster significance threshold of p=0.001

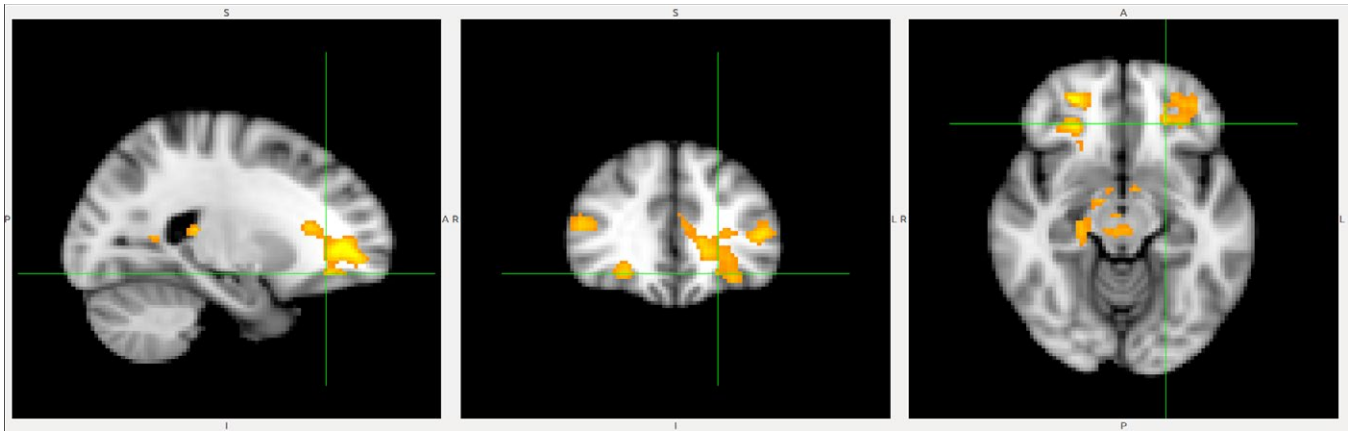

Figure 6a: Cocaine smokers compared to controls, showed increased activation in response to cocaine cues in left orbitofrontal cortex. Group-level *z* (Gaussianised *t*) statistic images were thresholded using clusters determined by z=1.65 and a (corrected) cluster significance threshold of p=0.001

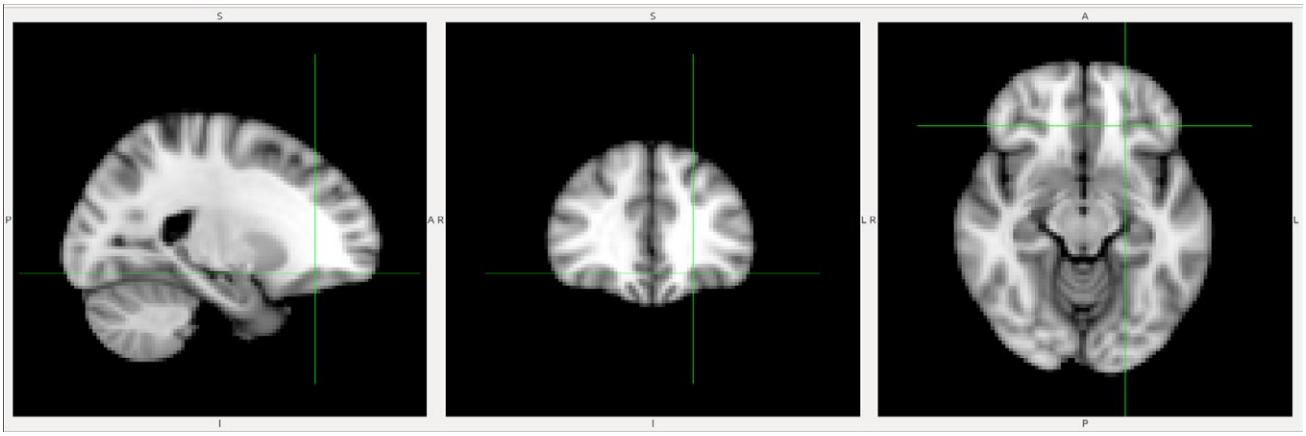

Figure 6b: Control participants' activation in left orbitofrontal cortex while they looked at cocaine cues.

*Group-level *z* (Gaussianised *t*) statistic images were thresholded using clusters determined by z=1.65 and a (corrected) cluster significance threshold of p=0.001

	Cocaine (n=20) Mean (SD)	Control (n=17) Mean (SD)	*t*-stats	*p*
Age (Years)	46 (6.4)	46 (7)	0.10	0.92
Education (Years)	13.4 (2.4)	13.5 (2.1)	-0.17	0.86
Race/Ethnicity				
Caucasian	7	5		
African American	11	11		
Hispanic	2	1		
Female (n)	5	4		
Cocaine Use				
Frequency (times/week)	3	N.A		
Duration of use (yrs.)	16	N.A		
Money Spent ($/week)	$220	N.A		
Alcohol Use				
Frequency (days/month)	1.9	4.0	-4.89	0.00*
Quantity (drinks/occasion)	2.1	1.7	0.92	0.37
Non-drinkers (#)	7	11		
Nicotine Use				
Frequency (days/week)	5.1	5.7	-0.40	0.70
Quantity (cigarettes/day)	6.3	2.8	2.00	0.07
Non-smokers (#)	7	11		
Caffeine Use				
Frequency (days/week)	4.4	3.6	0.78	0.44
Quantity (cups/day)	1.3	1.3	0.26	0.80
Non-caffeine users (#)	7	6		
Clinical Characteristics				
DSM-IV-R cocaine dependence	10	N.A		
DSM-IV-R cocaine abuse	3	N.A		

Note: *denotes significant group difference

Table 1: Demographic and substance use information for cocaine smokers and controls

Results showed that cocaine smokers compared to control participants showed significantly increased activation in response to cocaine cues in anterior cingulate gyrus, posterior cingulate gyrus, left insula, right amygdala, left precuneous and bilateral orbitofrontal cortex, caudate, parahippocampal gyrus, thalamus, frontal pole, and lingual gyrus (which lies within the occipital cortex) brain regions. However, when comparing cocaine smokers to controls no significant difference in activation to neutral cues was observed. These results are consistent with previous cocaine cue reactivity literature that showed that cocaine cues activate the anterior cingulate cortex, posterior cingulate cortex, insula, amygdala, orbitofrontal cortex, occipital cortex, and thalamus in chronic users of cocaine [3-11,20,21]. This study extends the earlier cocaine cue reactivity studies by examining brain areas activated in non-treatment seeking chronic smokers of cocaine in response to cocaine cues while they were unlikely in significant acute cocaine withdrawal. The current participants were scanned at least 72 hours since their last cocaine use and the negative urine test result for cocaine in all of them before scanning demonstrated that cocaine's primary active metabolite benzoylecgonine had left their system by the time they were scanned.

Results showed that the chronic cocaine smokers did not show a

Harvard-Oxford Cortical/Subcortical Atlas Label	z-value	X	Y	Z
Anterior Cingulate Cortex	2.52	-4	24	12
Posterior Cingulate Cortex	2.36	-4	-50	12
Left Insula	2.24	-26	26	12
Left Precuneus	1.79	-28	-64	12
Right Amygdala	2.57	16	-10	-16
Right Orbitofrontal Cortex	2.48	28	32	-12
Left Orbitofrontal Cortex	2.07	-22	34	-12
Right Caudate	1.84	12	26	-4
Left Caudate	1.98	-18	26	-4
Right Parahippocampal gyrus	2.35	12	-34	-4
Left Parahippocampal gyrus	1.77	-12	-34	-4
Right Thalamus	2.07	2	-10	10
Left Thalamus	2.14	-4	-10	10
Right Frontal Pole	2.76	32	46	2
Left Frontal Pole	2.80	-26	42	-4
Right Lingual Gyrus	1.88	12	-34	-6
Left Lingual Gyrus	1.82	-8	-40	-6

Note: Activation is described by a *z*-value, related to the intensity of activation and *x* ,*y*, *z* coordinates in standard MNI brain space. Group-level *z* (Gaussianised *t*) statistic images were thresholded using clusters determined by z = 1.65 and a (corrected) cluster significance threshold of *p* = .001.

Table 2: Brain areas that showed significantly increased activation in response to cocaine cues when cocaine smokers were compared to controls

significant positive correlation between the activation in the cocaine cue processing brain regions and subjective craving ratings. These results are in agreement with the previous studies that failed to show a significant positive correlation between activation in cocaine cue processing brain regions and craving ratings in cocaine users [21]. But the present results are in contrary to earlier studies that showed a significant positive correlation between brain activation and craving ratings in chronic users of cocaine [4,7,10]. One methodological difference may explain this contradictory finding. In the previous studies, the craving ratings were collected not while the participants viewed the cocaine cues but after they finished viewing them and before they left the laboratory, whereas in the present study the craving ratings were collected while they viewed the cocaine cues.

To summarize, in this study compared to control participants, an enhanced activation in brain areas such as cingulate cortex, insula, amygdala and orbitofrontal cortex in cocaine users in response to cocaine cues reflects cocaine users' increased salience to cocaine cues, and this enhancement may not indicate increased craving for cocaine. Future studies will examine how these brain areas are causally related while the cocaine users view cocaine related cues.

Finally, we need to discuss a few caveats while considering the results of the present study. First, although we made every effort to match the cocaine and control groups in terms of their age, educational and ethnic/racial background, it was not possible to match them exactly in terms of their alcohol use frequency (Table 1). Second, there were not enough female cocaine smokers (n=five) to examine the influence of sex on reactivity to cocaine cues. This important research question should be addressed in future studies. Despite these limitations, the results of the present study add important insight into the cocaine cue reactivity literature. The findings have important implications for cocaine treatment development.

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