Drugs and Alcohol Addiction

RESEARCH ARTICLE

An FMRI Study to Examine Recognition Memory for Appetitive Cocaine Picture Stimuli in Non-Treatment Seeking Cocaine Smokers

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Abstract

Background: Maintenance of problematic drug use is believed to be influenced by conscious explicit memory processing, such as the processing involved in recognition memory. Few studies have examined recognition memory in drug users, but it is not known whether this memory process becomes biased towards appetitive cues in substance abusing populations. In this functional magnetic resonance imaging (fMRI) study, we examined explicit recognition memory for cocaine and neutral picture stimuli in cocaine users and controls.

Methods: During the study phase of a recognition memory task, 20 non-treatments seeking, chronic cocaine smokers (15M; 5F) and 17 age-matched controls (13M; 4F) viewed cocaine and neutral picture cues. During test, participants were instructed to discriminate previously viewed and new cocaine and neutral cues one at a time. Blood oxygenation level dependent (BOLD) data were collected while participants indicated whether they previously had seen the cue.

Results: Cocaine users (vs. controls) showed a significantly enhanced activation in 10 brain regions during correct old/new recognition of cocaine (vs. neutral) cues. These areas in cocaine users included drug cue reactivity-related and recollection-based regions. Behavioral data showed that recognition accuracy (d') for cocaine cues was significantly greater in cocaine (vs. control) group; there were no group differences for neutral cues.

Conclusions: Behavioral data showed that recognition memory processing in cocaine users compared to controls was biased towards appetitive cocaine cues. Imaging results suggested that in cocaine users, but not controls, correct recognition of cocaine cues activated both drug cue reactivity-related and recollection-based areas that may promote cocaine use behavior.

Keywords: fMRI; Recognition memory; Cocaine smokers; Cocaine

Introduction

Explicit memory processes, also referred as controlled, episodic, or declarative memory [1], require attention and conscious awareness, and are often strategy-based. These processes are initiated intentionally and are influenced by encoding strategies and depth of processing [2]. One of the commonly studied explicit memory phenomena is recognition memory, measured as an individual's ability to correctly identify whether a stimulus has been seen previously or is 'new.' The ability to identify previously seen emotionally charged events and cues (i.e., memory bias), for example, is likely linked to efficiently negotiating the world and to survival [3]. Earlier studies in cognitive neuroscience have focused on identifying the neuronal networks that underlie explicit memory processing [4, 5]. The results of functional magnetic resonance imaging (fMRI) studies suggest that in healthy controls, correct recognition is associated with an increased activation in brain areas involved in conscious recollection [6, 7, 4, 8]. The brain regions that have been most often associated with correct recognition of previously presented stimuli are middle frontal gyrus, temporal and occipital regions [6, 7, 4, 5, 8]. Similar areas of temporal activation have been observed during correct recognition of previously seen faces [7] and words [8], and correct word recognition activated the middle frontal gyrus as well [8].

The recognition memory phenomenon has been little studied in substance abusing populations. We are aware of only one fMRI study that examined explicit recognition memory in cocaine smoking women who were additionally HIV-infected [9]. Meyer and colleagues found that compared to women who never used cocaine, activation in the bilateral prefrontal cortex was lower in current and former cocaine users during correct recognition of word stimuli that were neutral in nature. The questions of whether recognition memory is sub served by the

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same neural network in cocaine smokers as in healthy controls, and whether cocaine-related stimuli differentially facilitate explicit recognition compared to neutral stimuli may be particularly relevant to understanding visual drug cue reactivity in chronic cocaine and other drug users. Maintenance of drug use is believed to be influenced in part by explicit memory processing [10-12] and by appetitive cue reactivity [13]. Similar to emotional cues, appetitive cues, including drug and alcohol cues, can create attentional bias [14, 15], a mechanism that has received more research attention compared to memory bias mechanisms. These two biases have seldom been linked in the literature [16]. The demonstration of memory bias for drug cues over neutral cues would extend the growing drug cue exposure literature showing that exposure to drug cues can induce subjective craving as well as the reward network brain activation [13]. Fuller understanding of explicit memory bias in cocaine users towards appetitive cocaine stimuli compared to neutral stimuli will expand our understanding of the neurocognitive processes that support cocaine use behaviors and could further aid in designing intervention strategies.

The present study thus examined (1) whether in non-treatment seeking cocaine smokers', compared to non-cocaine using controls', explicit recognition memory was biased by appetitive cocaine-related compared to neutral picture cues, and (2) whether there is an increased neural activation in cocaine smokers compared to controls during correct old/new recognition of cocaine cues versus neutral cues. Correct recognition was examined using a recognition sensitivity measure d-prime (d′) defined as an individual's ability to correctly identify a picture cue that previously was viewed during the study phase as 'old' and to correctly identify a cue that had not previously been seen as 'new' [17].

This fMRI study was conducted in the context of a cue reactivity study [18], wherein we collected fMRI data during a recognition memory task from non-treatment seeking cocaine smokers who had been abstinent from cocaine for 72 hours and similarly-aged, healthy control participants with no cocaine experience. The use of picture cues in the present study was motivated by the finding that chronic drug and alcohol use behaviors are frequently triggered by the sight of substance-related cues in the environment. For example, the image of a favorite alcoholic drink induces alcohol craving due in part due to activation of past memories related to alcohol use in alcohol dependent individuals [19]. We hypothesized, due to increased salience of appetitive cocaine cues in chronic cocaine users compared to controls, that the cocaine users would demonstrate enhanced activation in cue reactivity related brain areas, such as the prefrontal and limbic brain regions [13] and also higher levels of recognition accuracy for cocaine cues compared to neutral cues due to the increased salience of appetitive cocaine cues in this group. Due to the lack of earlier drug cue recognition memory studies in cocaine users whose neurocognitive functioning is not complicated by HIV or other obfuscating conditions, we explored how the two groups differed in their activation of recollection-based brain areas, such as hippocampus and parahippocampal gyrus [5], middle frontal gyrus, and occipital regions, during the recognition memory task.

Methods

Participants

Twenty (15M; 5F) non-treatment seeking cocaine smokers who were abstinent from cocaine use for 72 hours, and 17 (13M; 4F) age-, education-, and ethnic background-matched healthy participants took part in the study. Participants were recruited from the Substance Use Research Center at Columbia University Medical Center, by advertising in local newspapers, and by word-of-mouth. 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. In this study, all cocaine smokers were only misusing cocaine. 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. Groups did not differ in alcohol use quantity, cigarette use frequency and quantity, and caffeine use frequency and quantity. Of the 20 cocaine smokers, 13 met a DSM-IV-R diagnosis of either abuse or dependence for cocaine, whereas 7 did not meet these diagnostic criteria as confirmed by SCID [20]. Although these seven individuals were heavy cocaine users, they were non-treatment seeking and thus reported no distress from their use, a defining feature of the diagnosis. On the day of scanning, all participants provided written informed consent approved by the Rutgers University Institutional Review Board, and were administered a urine screen to rule out pregnancy in women and to ensure negative urine toxicology for cocaine, methamphetamine, THC, opiates, and benzodiazepines (One Step Multi-Drug Screen Test Panel). They were also assessed for recent alcohol use with a breathalyzer. At the end of the day, participants were paid for their transportation and received a gift certificate worth $100 for their participation.

Stimuli

Study Phase of the Recognition Memory Task. Participants viewed 30 cocaine-related picture stimuli (15 unique stimuli that were presented twice) and 30 neutral picture stimuli (15 unique stimuli that were presented twice). Cocaine stimuli, selected from pictures kindly supplied by Dr. Rita Goldstein (Icahn School of Medicine, Mount Sinai) and Dr. Robert Hester (The University of Melbourne), included pictures of smoke able cocaine, paraphernalia, and people smoking cocaine. Examples of neutral stimuli included pictures of nature scenes [21, 22]. Neutral stimuli were selected from non-copyrighted images on the internet. These stimuli are available on request from the author. Cocaine and neutral stimuli were matched in terms of complexity. Test phase of the Recognition Memory Task. A total of 60 picture stimuli were used: 15 previously

viewed and 15 new cocaine picture stimuli, and 15 previously viewed and 15 new neutral picture stimuli.

Procedure

Recognition Memory Task

Study Phase

During the study phase of the recognition memory task, participants viewed two blocks of cocaine picture cues and two blocks of neutral picture cues presented in a counterbalanced manner across participants, with the constraint that two blocks of the same stimulus type were not presented in succession. Stimuli (either cocaine or neutral) presented in the first block were repeated in the second block. Each stimuli block (15 cocaine or neutral picture cues) lasted for 90 seconds. Stimuli within the blocks were randomly presented and each stimulus was presented for 4 seconds followed by a fixation cross that remained for 2 seconds. A trigger pulse from the MRI console was used to synchronize stimulus presentation with fMRI acquisition. These fMRI cue reactivity data have been reported in Ray et al. [18]. After the study phase was completed, participants took part in a picture/non-picture decision paradigm which utilized a completely separate set of pictures and served as a distractor prior to the recognition memory task.

Test phase

During the test phase of the recognition memory task, participants viewed the 60 picture cues in a random order. Each cue appeared for 4 seconds on the screen and the participant indicated whether or not he/she previously had seen the cue during the study phase by pressing the appropriate mouse button. A trigger pulse from the MRI console was used to synchronize stimulus presentation with fMRI acquisition. The task was developed using E-prime (Psychology Software Tools, Inc., Pittsburgh, PA). Finally, participants' cocaine craving ratings were collected at the completion of the fMRI recognition session using the 10-item CCQ-Brief questionnaire [23].

Image Acquisition

A 3T Siemens Trio scanner and Siemens 12 channel head coil were used to acquire the fMRI data. Functional imaging was done using a single-shot gradient echo-planar EPI sequence (TR=2000 ms, TE=25 ms, flip angle=90°, matrix=64x64, FOV=192 mm). Thirty-five contiguous oblique axial slices (1 mm gap; 3x3x3 mm voxels) parallel to the AC-PC line were obtained. Anatomical images were acquired using a T1-weighted protocol (TR=1900 ms, TE=2.52 ms, matrix=256x256, FOV=256 mm, 176 1-mm sagittal slices with .5 mm gap) [18].

Image Analysis

Image preprocessing and data analysis were performed using FSL 6.00 software (FMIRB's Software Library, www.fmirb.ox.ac.uk/fsl). Registration to high resolution structural and/or standard space images was carried out using FLIRT [24, 25]. Functional images were high-pass filtered (Gaussian-weighted least-squares straight line fitting, with sigma = 25.0s); skull stripped using BET [26] ; motion corrected using MCFLIRT [25]; and smoothed using a Gaussian kernel of FWHM 6 mm. No slice timing correction procedure was used for the following reasons:

i. the hemodynamic response of 6-20 seconds makes slice timing correction for short TRs (in the present study, it is 2 seconds) irrelevant, and

ii. FSL, the software we used to conduct data analysis, does not recommend using slice timing correction [18]. Participants displaying higher than 1 mm mean frame-wise displacement were planned to be removed from further analysis.

To model correct recognition (or recognition accuracy) for cocaine and neutral cues, a Gaussian hemodynamic response function (HRF) and its temporal derivatives were applied to the basic waveform. Blood oxygenation level dependent (BOLD) scans for each participant were registered first to his or her high-resolution anatomical (MPRAGE) scan, and then registered to standard space using the FSL's MNI (Montreal Neurologic Institute) template. A two-level statistical analysis approach was used. The first level analysis was directed at brain activity related to recognition accuracy for cue type, that is, cocaine cues versus neutral cues. At the first level, two predictors were coded to represent mean activation while we measured recognition accuracy for cocaine cues and that for neutral cues. Mean brain activation was analyzed by a GLM for each predictor in individual participants using FEAT (FMRI Expert Analysis Tool). Moreover, the cocaine cues predictor was contrasted to the neutral cues predictor: cocaine cues > neutral cues. The results were then entered into a higher (i.e., group) level analysis using FLAME 1 mixed-effects [39]. 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) for a total of 33 participants. Group level statistic images were thresholded using clusters determined by $z > 2.33$ and a (corrected) cluster significance threshold of $p < .001$ [26].

Behavioral Data Analysis

Mean accuracy and error rates for the cocaine and neutral picture cue categories were calculated for each participant. Accuracy rates consisted of hit rates and correct rejection rates. Error rates consisted of false positive response rates and miss response rates. False positives were defined as the number of new picture cues that were mistakenly recognized as seen in the study phase. Misses were defined as the number of pictures previously seen in the study phase that the participant failed to recognize. Hit and false positive rates were computed for each picture cue category. A signal detection measure of recognition sensitivity (d′) was obtained from these ratings [27, 17]. D-prime (d′) was defined as an individual's ability to correctly identify a picture cue that previously was viewed during the study phase as 'old' and to correctly identify a cue

that had not previously been seen as 'new' [17]. A repeated measures analysis of variance (ANOVA) was conducted to examine the effects of picture cue type (two within subjects repeated measures: neutral and cocaine), group (two between-subject conditions: cocaine and control), and their interaction on recognition memory performance. Whether memory for the two picture cue categories was different across the two groups was tested by the within-subject-by-between-subject interaction terms.

Results

Imaging Results

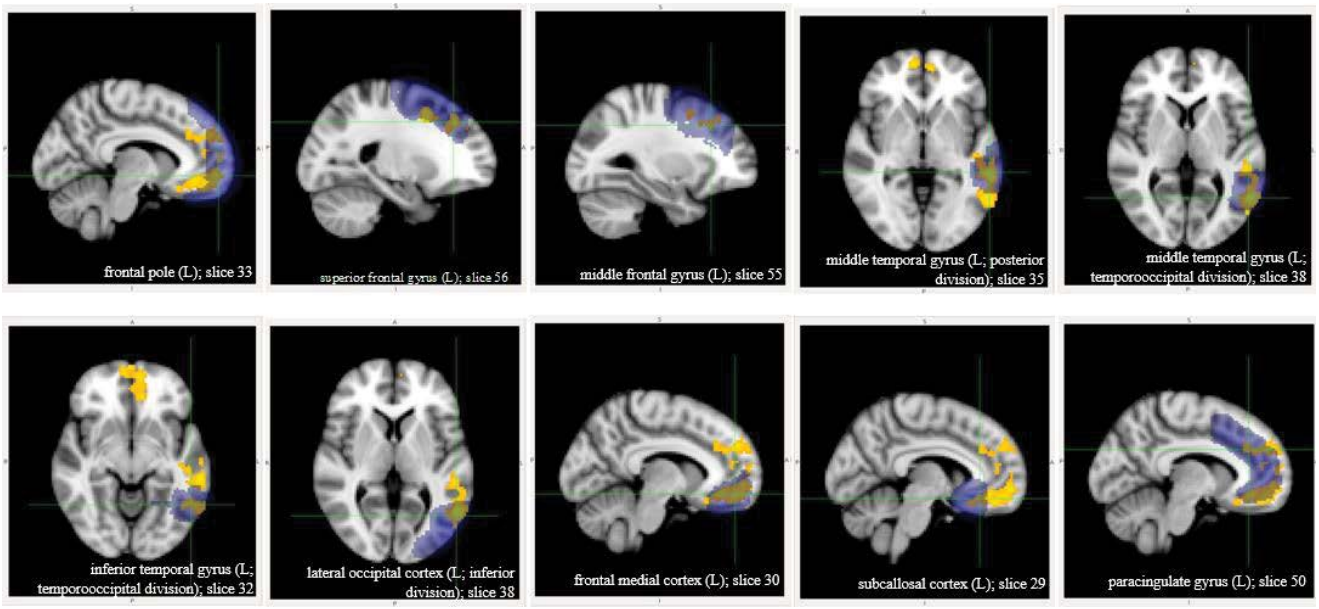
One cocaine participant's data were excluded from the analysis as he/she did not perform the recognition memory task (n = 19). Three control participants' fMRI data were excluded from the analysis: one for excessive head motion and two for technical failure (n = 14). For the cocaine group, the mean absolute displacement was .20 millimeters (mm) (SD = .09 mm) and the mean relative displacement was .13 mm (SD = .06 mm). For the control group, the mean absolute displacement was .23 mm (SD = .27 mm) and the mean relative displacement was .13 mm (SD = .10 mm). A group level independent sample t-tests revealed that groups did not differ in mean absolute displacement ($p = 0.702$) or mean relative displacement ($p = 0.885$). As shown in Figure 1, group level analysis revealed that cocaine users compared to controls showed significantly enhanced activation in 10 brain areas when recognition accuracy was measured for cocaine cues compared to neutral cues (2 significant clusters; cluster sizes = 1677 voxels and 1834 voxels): frontal pole (bilateral); superior frontal gyrus (left); middle frontal gyrus (left); middle temporal gyrus-posterior division (left); middle temporal gyrus-temporooccipital part (left); inferior temporal gyrus-tempooccipital part (left); lateral occipital cortex-inferior division (left); frontal medial cortex (left); subcallosal cortex (left); paracingulate gyrus (left) (Table 1). The anatomical ROI masks from the Harvard-Oxford Cortical and the Harvard-Oxford Subcortical Structural Atlases implemented in FSLView were used to identify the 10 brain areas. In contrast, the control group did not show any significant activation in frontal medial cortex, subcallosal cortex, and paracingulate gyrus (cue reactivity-related areas) when recognition accuracy was measured for cocaine cues.

The group level analysis further showed that cocaine users compared to controls did not show significantly lower activation in any brain area even at the lowest activation threshold ($z > 1.65$, $p < .05$) while recognition accuracy was measured for neutral visual cues, contrary to Meyer and colleagues (2014).

Behavioral Results

There was no significant main effect of picture cue type [$F(1, 34) = .16$, $p = .69$] or group [$F(1, 34) = 1.00$, $p = .32$] on recognition sensitivity. The interaction between picture cue type and group was significant, $F(1, 34) = 14.13$, $p = .001$, partial eta2 = .294 (see Figure 2). As shown in Figure 2, correct recognition (measured in terms of d′) for cocaine cues was significantly greater in the cocaine group compared to the control group, $t(34) = 3.11$, $p < .01$. No group differences were observed for neutral cues. Analysis of the craving data showed that cocaine users rated their craving state higher than did controls [$t(34) = 6.09$, $p < 0.001$; 3.27 (SD = 1.49) vs. 1 (SD = 0)].

Discussion



Note: Slices are in z direction.

Blue colored areas indicate anatomical ROI masks from the Harvard-Oxford Cortical Structural Atlases implemented in FSL View. Anatomical ROI masks are overlaid onto the activation.

Figure 1: Brain areas that showed a significantly enhanced activation (orange) in cocaine users (vs. controls) while recognition accuracy was measured for cocaine (vs. neutral) cues.

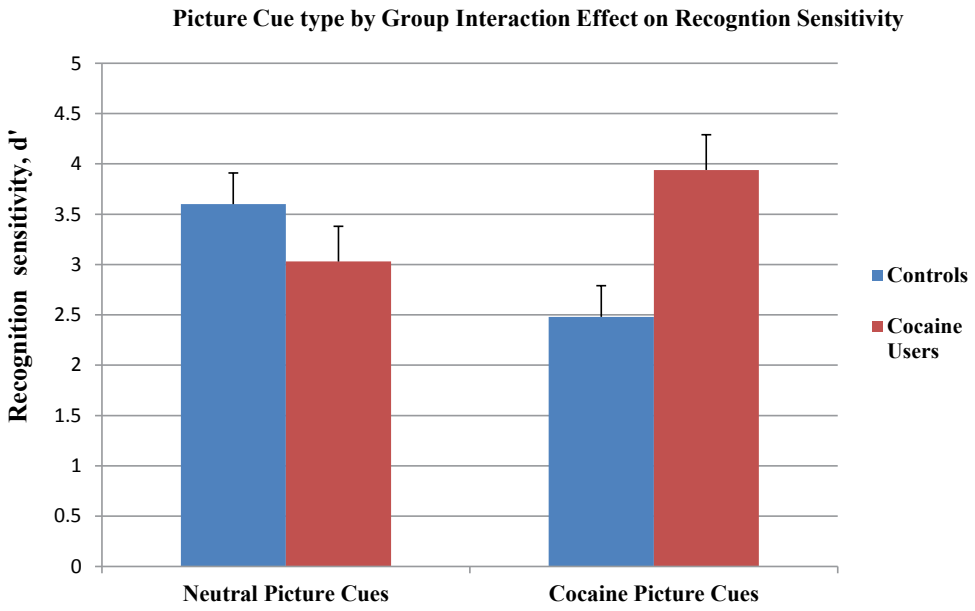
Harvard-Oxford Cortical/Subcortical Atlas Label	z-value	x	y	z
Frontal Pole	-	-	-	-
Right	2.74	6	62	-6
Left	2.94	-8	58	-6
Superior Frontal Gyrus (L)	2.9	-22	32	40
Middle Frontal Gyrus (L)	2.73	-28	26	38
Middle Temporal Gyrus posterior division (L)	3.31	-58	-36	-2
Middle Temporal Gyrus temporooccipital part (L)	3.41	-54	-60	4
Inferior Temporal Gyrus temporooccipital part (L)	2.84	-52	-56	-8
Lateral Occipital cortex inferior division (L)	3.18	-54	-64	4
Frontal Medial Cortex (L)	2.91	-8	48	-12
Subcallosal Cortex (L)	2.56	-6	30	-14
Paracingulate gyrus (L)	2.51	-8	34	28

Note: L= Left.

The anatomical ROI masks from the Harvard-Oxford Cortical and the Harvard-Oxford Subcortical Structural Atlases implemented in FSLView were used to identify the brain areas.

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 statistic images were thresholded using clusters determined by $z > 2.33$ and a (corrected) cluster significance threshold of $p < 0.001$.

Table 1: Ten brain areas that showed a significantly enhanced activation in cocaine users compared to controls while measuring correct recognition for cocaine cues relative to neutral cues.



Note: Error bars represent standard error of mean.

Figure 2: Correct recognition measured in term of recognition sensitivity (d') for cocaine cues was significantly greater in the cocaine group compared to the control group. No significant group differences were observed for neutral cues.

The overall objective of this study was to examine behavioral and neural correlates of explicit recognition memory for appetitive cocaine and neutral picture cues in non-treatment seeking chronic cocaine users compared to controls. During the study phase of the recognition memory task, participants viewed cocaine and neutral picture cues. During the test phase of the recognition memory task, they were asked to indicate whether they had seen the cue earlier in the study. Consistent with the hypothesis, the cocaine users compared to controls demonstrated significantly enhanced activation in prefrontal and limbic cue reactivity-related brain areas while correct recognition was measured for cocaine visual cues compared to neutral visual cues. In fact, the control group showed no significant activation in these cue reactivity areas. In addition to the drug cue reactivity-related areas, chronic smokers of cocaine compared to controls also demonstrated increased activation in recollection-based brain areas such as the middle frontal gyrus, temporal, and occipital regions when

correctly recognizing cocaine picture cues relative to neutral picture cues. This finding for recollection-based brain areas is consistent with the results of earlier studies that investigated neural underpinnings of the explicit recognition memory phenomenon in healthy controls [4-8]. To our knowledge, this is the first fMRI study that examined explicit recognition memory of appetitive cocaine and neutral stimuli in chronic cocaine users by utilizing a visual cue memory task.

The present results extend the addiction cognitive neuroscience literature by demonstrating that in chronic cocaine smokers, explicit recognition of appetitive cocaine-related cues not only produces activation in recollection-based brain areas, but it also produces activation in the drug cue reactivity-related brain areas. More specifically, cocaine users (vs. controls) showed an enhanced activation in prefrontal and limbic cue reactivity-related brain areas, such as frontal medial cortex, subcallosal cortex, and paracingulate gyrus, that have been associated with drug cue reactivity [19, 13, 18]. Notably, the involvement of subcallosal cortex in chronic users of cocaine during explicit recognition of cocaine picture cues suggests activation of a motivational/drive circuit which plays an essential role in drug addiction [29]. According to neurobiological models of addiction, memory processes play a crucial role in the development and maintenance of drug abuse [11, 30, 31]. These models highlight the critical role of associative and conditioned learning processes through which repeated reward experiences become paired with antecedent environmental stimuli. Over time, neural response to reward occurs in anticipation of the drug whenever drug-associated stimuli are encountered [31]. We posit that explicit memory processes such as recognition memory, which occur simultaneously with reward network activation, may pave the path to, and continue to interact with, the non-effortful associative memory processes through which drug cues develop salience over time.

That is, explicit memory for environmental stimuli such as visual drug paraphernalia, locations of use, and social aspects of use would be an initial form of experience-dependent learning that occurs prior to reward experiences being repeatedly paired with environmental stimuli. Then, as many experiences of reward become mapped to cues during repeated episodes of drug use, these stimulus cues acquire salience to that individual. The present results suggest that explicit memory processes such as recognition accuracy remain operative in parallel with the anticipatory brain responses that have been observed to conditioned stimuli [31] in chronic cocaine users. Future studies using an effective connectivity analysis approach are needed to examine the causal relationship between the recollection-based and drug cue reactivity-related brain areas while a cocaine user is engaged in memory tasks [32, 33].

The one previous addiction neuroimaging study that examined explicit recognition memory in cocaine users (HIV-infected) observed that activation in bilateral prefrontal cortex, specifically the frontal medial cortex, was significantly higher in women who had never used cocaine (compared to current and former crack cocaine users) during recognition of neutral verbal stimuli [9]. Our results, however, did not show any increased activation in control participants (compared to cocaine users) while recognition accuracy was measured for neutral stimuli, even when the activation was set at the lowest threshold. The discrepancy in findings may be explained by differences between Meyer et al. and the present study. In Meyer et al.'s sample, brain effects of cocaine smoking were complicated by HIV status, which is also associated with neural changes [9]. As well, Meyer and colleagues used neutral verbal stimuli, whereas the present study compared recognition accuracy of cocaine compared to neutral picture stimuli. In addition, Meyer et al. [9] sample included all women and some of them were not using cocaine currently.

It should be noted that the present results represent recollection-, rather than familiarity-, based recognition memory. According to dual process theories of recognition, recognition memory judgments can rely on two distinct processes: recollection and familiarity [27, 34, 35]. Recollection is thought to be an explicit, attention demanding search process, whereas familiarity is a more implicit, automatic process. Specifically, recollection entails conscious retrieval of details associated with an item when it was initially presented, whereas familiarity refers to the knowledge or awareness of a particular item, but not being able to recall specific information associated with its initial presentation [36] This distinction can be illustrated through a common experience such as recognizing an individual who is familiar, but not being able to recollect previous interaction(s) with him/her. In this study, during the test phase, participants explicitly were asked to indicate whether or not they had previously seen the cues during the study phase. This task entails a conscious retrieval of the information, that is, whether or not the cue was present in the study phase [36]. The fact that the present recognition memory task was recollection-based is further supported by a lack of observed activation in brain areas such as precuneus, bilateral middle occipital, and left fusiform gyrus that have been associated with familiarity-based recognition memory [6].

Consistent with the imaging data, the behavioral data from the recognition memory task showed that the cocaine (vs. control) group had significantly greater recognition accuracy for cocaine picture cues. No group differences were observed in recognition accuracy for neutral picture cues. Thus, the behavioral data indicated that recognition memory processing in chronic cocaine users is biased towards appetitive cocaine cues. The present results extend Wiers and colleagues [37] study that demonstrated increased explicit cocaine-related memory associations in a group of treatment seeking cocaine-dependent polysubstance users compared to control participants by using an expectancy questionnaire and verbal stimuli. The equivalent recognition memory performance for the neutral picture cues between the two groups in the current study is consistent with the results of Simon and colleagues [38] who also observed no significant difference between a treatment seeking cocaine and a control group in terms of recognition memory for neutral picture cues. The study has several strengths: first, all cocaine

smokers were current cocaine users with confirmed abstinence. Second, the cocaine and the control groups were matched in terms of age, educational and ethnic/racial background. A few caveats should also be considered in interpreting the results of this study. First, frequency of alcohol use was about double in the control compared to the cocaine group (4 days/month versus 1.9 days/month). Nonetheless, average alcohol use was low for both groups (<1 drink/day).

Second, there were not enough female cocaine smokers (n=5) to examine the influence of sex on recognition memory for cocaine related picture cues behaviorally or in terms of brain functioning. Future studies would benefit from including larger numbers of women to examine potential sex differences in explicit memory processing of drug cues in different drug populations using both behavioral and imaging paradigms. Despite these limitations, the present fMRI and behavioral results provide a valid test of explicit recognition memory for cocaine picture cues in a group of non-treatment seeking cocaine users without other known neurological disease. Generalizability of the present findings can be tested in future studies with other drug abusing samples. In conclusion, this study suggests that better understanding of the interplay between effortful explicit memory processes, reward network activation and the non-effortful associative learning processes which contribute to development of drug cue salience will be helpful in developing better prevention and intervention strategies for individuals with cocaine use and other substance use disorders.

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