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An fMRI Study of the Interaction of Stress and Cocaine Cues on Cocaine Craving in Cocaine-Dependent Men

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Acute stress is associated with relapse in cocaine addiction, possibly through the activation of craving-related neural circuitry. Neural responses to cocaine cues and acute stress were investigated in an fMRI study. Ten male participants mentally reenacted personalized scripts about cocaine use and a neutral experience both with and without a stressor present (anticipation of electrical shock). Interaction analysis between script type and stress condition revealed greater activation of the posterior cingulate cortex and of the parietal lobe during the cocaine script in the presence of the stressor. These data suggest that stress may precipitate relapse in cocaine addiction by activating brain areas that mediate reward processing and the attentional and mnemonic bias for drug use reminders. (Am J Addict 2007;16:174–182)

INTRODUCTION

The treatment of cocaine dependence is difficult because of the chronically relapsing course many patients exhibit. Often these patients cycle for years between periods of cocaine use, detoxification, abstinence, relapse, and reinstatement of heavy use. Stressful life events and concomitant negative emotional states are often factors that lead to relapse.[1,2] Recent attempts to better model the addiction process are integrating our understanding of drug reward, motivation, and neural circuits mediating stress responses.[3–6] These models emphasize drug addiction as a chronic dysregulation of reward pathways that is perpetuated by stress responses involving dopaminergic and neuroendocrine systems. Preclinical data support the importance of stress responses in cocaine addiction. Cocaine self-administration paradigms are widely used as models of drug addiction. Footshock stress enhances the acquisition of stimulant self-administration[7] and provokes the reinstatement of cocaine self-administration.[8,9] Sinha et al.[10] modeled this phenomenon in human subjects in a laboratory setting by demonstrating in two separate paradigms that stress led to the emergence of cocaine craving in cocaine abusers.

Advances in functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) permit the identification of brain areas activated during cocaine craving. The areas showing activation include limbic areas implicated in motivation and emotion as well as areas functionally connected to the mesocorticolimbic dopamine system: anterior cingulate cortex, amygdala, nucleus accumbens, and insula.[11–17]

The neural response to stress can likewise be localized successfully using fMRI technology. Phelps et al.[18,19] reported the activation of the amygdala in normal humans during conditions of threat of shock compared to safe conditions. This work complements the large body of preclinical work indicating the importance of the amygdala and the bed nucleus of the stria terminalis (BNST) in fear or anxiety.[20,21]

One published study investigated the effects of stress on cocaine craving with functional imaging. Li et al.[22] reported that female cocaine users had increased activations of frontal, cingulate, and insular cortex during script-guided imagery of stressful situations. In order to

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expand on this line of experimentation, the current study sought to elicit cocaine craving with cocaine cues presented during stress in order to simulate the confluence of stress and cocaine cues often faced by cocaine-dependent patients in periods leading up to cocaine relapse. Such a design would allow the investigation of effects of current stress on cue-induced cocaine craving and on brain regions thought to be involved in craving. Therefore, in light of clinical evidence of stress-precipitating cocaine relapse, and against the background of overlap of neural circuitry mediating drug reward and stress responses,[7] fMRI was used to study activations of relevant brain regions during a stress condition (threat of shock) presented concomitantly with cocaine cues designed to elicit craving. The a priori hypothesis was that stressful stimuli would enhance the activation of craving-related neural pathways.

METHODS

Participants

Ten males with cocaine dependence and in an early stage of drug abstinence participated in the study. All participants gave written informed consent to participate in a protocol approved by the institutional review boards of Emory University and the Atlanta VAMC. Participants met DSM-IV criteria for cocaine dependence and had no other current Axis I diagnoses, with the exception of substance-induced mood disorder or substance-induced mood disorder with psychotic features, as determined by the Structured Clinical Interview for DSM-IV (SCID). All participants' method of cocaine administration was through freebase (crack) smoking. Current abstinence from cocaine use was determined by self-report and a urine drug screen (Testcup Pro 5, Varian, Inc.). No other drugs of abuse were reported or detected by urine drug screen. Individuals with neurological disorders or unstable medical disorders were excluded from the study. All participants were right-handed African American males. Participants' demographic characteristics and cocaine use history are shown in Table 1. Participants were also screened for visual acuity by means of an eye chart and hearing by means of an audiometer (Grason-Stadler, Model GS1710). No participants were excluded for impaired vision or hearing.

TABLE 1. Demographic characteristics

	Mean (SD)	Range
Age in years	43.6 (3.8)	37–49
Education in years	14.2 (1.5)	11–16
Days clean	8 (4.9)	2–15
Years of use	15.9 (6.2)	6–27
Cost per month ($)	1,139 (1,311)	125–4,000

n = 10, except cost per month, where n = 7.

Baseline Assessments

A baseline assessment was performed for cocaine craving (University of Minnesota Cocaine Craving Scale, CCS[23]), mental imagery ability (Betts' Questionnaire on Mental Imagery, QMI[24]), nicotine dependence,[25] handedness,[26] current psychopathology (Brief Psychiatric Rating Scale, BPRS[27]), and ADHD symptoms (Conners Adult ADHD Rating Scale, CAARS-S:L[28]). The mental imagery ability of participants was assessed using the Betts' QMI.[24] This scale requires respondents to rate the vividness with which the subject can mentally image sensory and motor experiences, such as picturing a friend, hearing a train whistle, or feeling sand. Respondents used a seven-point scale ranging from a rating of 1, which represented an image that is ''perfectly clear and as vivid as the actual experience,'' to a rating of 7, which corresponds to ''no image at all.'' Therefore, a lower score on the QMI indicates a higher level of mental imagery ability.

Script and Shock Procedures

Script-guided mental imagery was used to evoke cocaine craving. Scripts were constructed using a modified version of the Vietnam Stressful Scene Construction Questionnaire[29] and following the methods of Sinha et al.[30] and Kilts et al.[15] Participants listened to and mentally reenacted a script composed from a self-reported sensations checklist and narratives of environmental contexts of personal drug-use experiences. A second script was also composed consisting of an emotion- and drug-neutral experience, that of getting up and dressed in the morning. Scripts were edited and time-adjusted to exactly 90 seconds using Sound Edit 16 software for Macintosh (version 2). The presentation of each script was preceded by a 60-second baseline period. There was a two-minute resting period between the presentation of the neutral and cocaine scripts. For purposes of analysis, each 90-second script was segmented into early (first 45 seconds) and late (last 45 seconds) components. This analysis plan reflected the uncertainty as to whether the early or late components of the script might elicit the strongest drug-craving response and related neural activations.

Each script was presented once (neutral script followed by cocaine script) during a stressor condition and again in a no-stressor condition in a counterbalanced fashion. The stressor consisted of the threat of a mild electrical shock to the wrist.[18] Just prior to the scan, they were told during which half of the session the shock(s) would occur. Subjects randomized to first receive the no-shock condition were told as they were positioned in the scanner that they would have no electrodes on and would not receive a shock until the second half of the session. A five-minute rest period was present between the threat of shock conditions, during which participants were presented with a common distractor task (asked to generate the names of as many animals as possible and in some cases to also count backwards from 100) for the purpose of returning

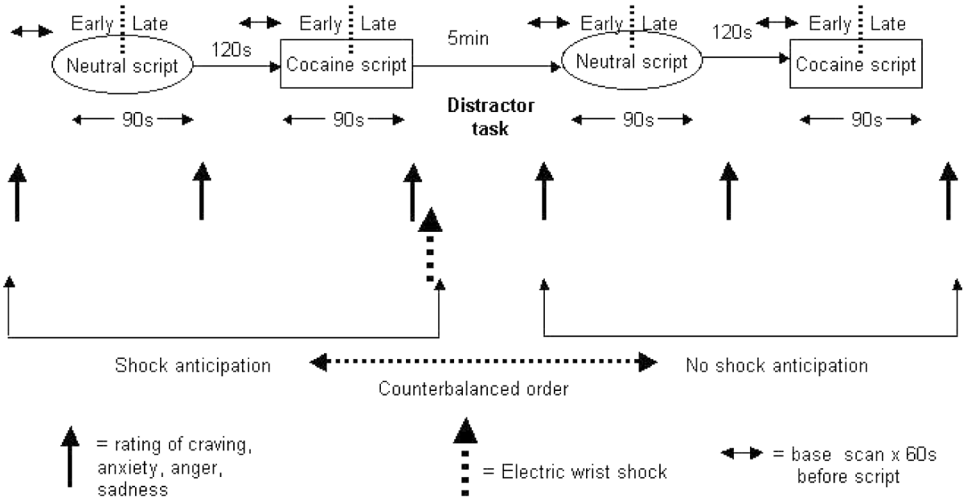

FIGURE 1. Time Course of Events during fMRI Study Protocol

them to a baseline emotional state and minimizing carry-over effects. At the end of this interval between the first and second halves of the session, electrodes were placed on their wrist, and they were reminded that they would receive from one to three shocks at any time during that half of the scan. For subjects randomized to receive shock during the first half, electrodes were placed on their wrist as they were first situated in the scanner and they were reminded that they would receive from one to three shocks at any time during that half of the session. During the five minutes between halves of the session, after the distractor task, electrodes were removed, and they were reminded that they would receive no further shocks. A single shock was administered upon the completion of the last script in the stressor condition.

Participants were asked to rate their subjective level of craving on a 100-point visual analog scale (ranging from 1 being "not at all" to 100 being "the most I've ever felt") at the end of each baseline period, immediately after completion of the neutral scripts, and again after completion of the cocaine scripts. Similar analog scales were used to assess the level of anxiety, sadness, or anger associated with script imagery. Figure 1 outlines the time course of events during fMRI scanning.

fMRI Scanning

Blood oxygen level-dependent (BOLD) fMRI was performed on a Siemens Trio 3 T MRI scanner. Foam padding was used to restrict the participants' head motion within the magnet. The functional images were obtained using a T2* weighted EPI pulse sequence (TR 2000 ms, TE 30 ms, flip angle 90 deg). Thirty contiguous axial slices with a slice thickness of 3 mm were acquired. In addition, an anatomical 3-D MP-RAGE sequence[31] was collected at an isotropic resolution of $1 \times 1 \times 1$ for 3-D analysis and visualization of task-related activations.

fMRI Image Processing and Analysis

Image pre-processing and data analyses were performed with statistical parametric mapping software (SPM 99; http://www.fil.ion.ucl.ac.uk/spm/) in Matlab 6.1.[32] Images were corrected for motion by registration to the first functional image obtained and spatially normalized to the Montreal Neurological Institute template. Images were smoothed using a Gaussian kernal (8 mm FWHM). Cerebral blood flow responses were modeled using the standard hemodynamic response function. All analyses were conducted using a fixed effects model with the threshold for significance set at 0.005 (uncorrected). Scans collected during scripts were divided into early (first 45 s) and late (second 45 s) components for purposes of analysis in a manner similar to that of Wexler et al. (2001).[16] That study reported interindividual variability in the time course responses to videotapes depicting cocaine cues; a similar variability was expected in the current study.

RESULTS

Baseline Assessments

Participant's average intensity of reported cocaine craving during the week prior to the scanning session was 4.85 on the 11-point scale of the CCS,[23] indicating a moderate level of cocaine craving (see Table 2). Participants also varied in their daily frequency of craving episodes during this period. Five participants reported experiencing 3–5 craving episodes per day, two participants reported having 6–10 episodes, and the remaining

TABLE 2. Baseline assessment outcomes

Measure	Mean (SD)	Range
CCS—cocaine craving	4.85 (2.4)	1–10
QMI	59.4 (31)	35–116
CAARS-SL	12.11 (8.4)	2–24
BPRS	26.2 (6.6)	19–38

three participants reported experiencing 0, 2, and greater than 20 craving episodes per day. Craving episodes were reported by 5 participants to last for 5 minutes or less and by 2 participants to last for 6–10 minutes. The remaining three participants reported longer average craving episodes of 31–45, 46–60, and 60–120 minutes. Six participants rated their drug cravings as having decreased in the prior week while four participants reported that their cravings had not changed in the prior week. None of the participants reported an increase in craving. The mental imagery ability of participants as assessed using the QMI indicated an above average mental imagery ability for the group as a whole (see Table 2). Participant scores on the BPRS (1–7 scale) indicated very mild current psychopathology (see Table 2). No participant reported a significant level of ADHD symptoms on the CAARS-SL (scores below the 75th percentile on the G scale were classified as being in the normal range).

Subjective Ratings of Responses to Script Imagery

Figure 2 illustrates the self-rated cocaine craving responses to script imagery on a 100-point scale for the subjects across the fMRI session. An ANOVA conducted on cocaine craving scores with a within-subjects factor of shock condition (two levels: shock and no-shock) and a within-subjects factor of timepoint (three levels: baseline, neutral script, and cocaine script) was significant for timepoint ($F(1,9) = 4.48$, $p = 0.02$), indicating that craving responses differed across the script types. Post-hoc tests on the main effect of timepoint indicated that cocaine craving after the cocaine script was significantly higher than craving at baseline ($p = 0.01$) and significantly higher than after the neutral script ($p = 0.03$). Across the three timepoints, cocaine craving during shock expectation did not significantly differ from that during the no-shock half of the session ($F(1,9) = 0.002$, $p = 0.97$). Craving at baseline during the shock portion of the session was numerically, but not statistically, higher than craving at baseline during the no-shock half of the session (post-hoc Newman-Keuls, $p = 0.38$). The interaction of timepoint and shock condition was not significant ($F(2,18) = 0.78$, $p = 0.47$). There were no significant changes at any timepoint during the session in subjective ratings of sadness, anxiety, or anger.

fMRI Analyses

Cocaine Scripts Compared to Neutral Scripts

The comparison of neural responses to neutral vs. cocaine scripts was performed using three approaches, with responses pooled for the shock and no shock conditions. In the first approach, responses in the first 45 seconds (“early”) of the neutral and cocaine scripts were compared (see Table 3). Significant cocaine cue-related activations were seen in the anterior cingulate cortex, insula, and posterior cingulate cortex. In the second approach, the last half of the scripts was compared. Significant activations were observed in the anterior cingulate cortex and insula (Table 3). The third analysis subtracted activations for the entire neutral scripts from the entire cocaine scripts. Cocaine cue-induced activations of anterior cingulate cortex, insula, and posterior cingulate cortex were

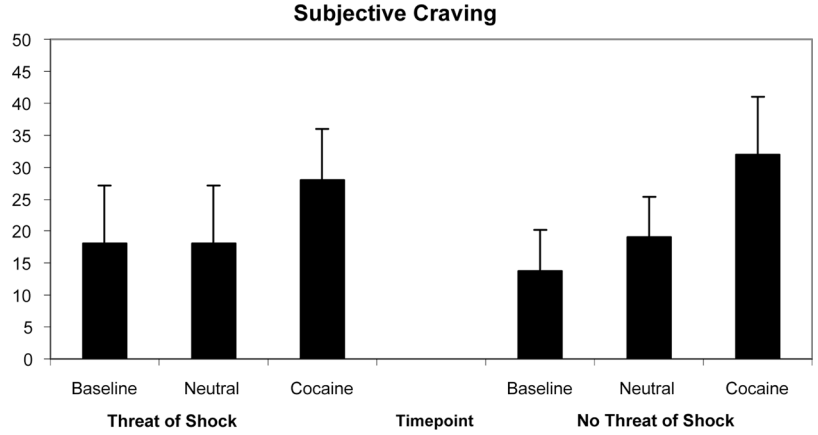

FIGURE 2. Craving Self-Reported by 100 mm Visual Analogue Scale During fMRI Scans (Means ± SEM). Baseline is 60 s Prior to Scripts. Neutral and Cocaine Refers to Content of Personalized Script Presentation. ANOVA: Significant for Timepoint ($F(1,9) = 4.48$, $p = 0.02$); not Significant for Shock Condition ($F(1,9) = 0.002$, $p = 0.97$) nor for Interaction of Timepoint and Shock Condition ($F(2,18) = 0.78$, $p = 0.47$)

TABLE 3. Location of neural activations for cocaine compared to neutral cues

Contrast	Area description	Broadmann's area	Number of voxels	T value	MNI coordinates* x, y, z
Early cocaine > Early neutral	Anterior cingulate	24	104	3.62	10, 26, 16
	Insula (L)	13	230	3.68	−40, −24, 22
	Posterior cingulate	31	41	3.34	12, −36, 30
Late cocaine > Late neutral	Anterior cingulate	24	10	2.81	8, 22, 18
	Insula	13	16	3.06	−40, −24, 22
Early + late cocaine >	Anterior cingulate	24	47	3.23	8, 22, 16
Early + late neutral	Insula (L, Figure 3A)	13	34	3.23	−40, −24, 22
	Posterior cingulate	31	12	3.00	12, −36, 30

*Distance (in millimeters) from the midsagittal plane (x coordinates, negative values refer to effects in the left hemisphere), anterior/posterior to the anterior commissure (y coordinates), and superior/inferior to the anterior/posterior commissure plane (z coordinates).

again observed (see Table 3); responses for the anterior and posterior cingulate cortex, left insula, and thalamus are illustrated in Figure 3.

Comparing Stressor to No-Stressor Conditions

Additional script response comparisons evaluated differences in the neural correlates of cue-induced cocaine craving during the stress condition compared to the no-stress condition. First, a comparison of the neural response to cocaine script imagery (early plus late components) during the no-stress condition relative to the cocaine script in the shock anticipation (stress) condition revealed right thalamus and precuneus/posterior cingulate cortex activation (see Table 4, "Early + late cocaine script with stress > Early + late cocaine script without stress"). Second, when the entire cocaine script plus its preceding baseline period was compared in the stress condition to the no-stress condition, significant activations of the genual anterior cingulate, right thalamus, and precuneus/posterior cingulate cortex were observed (see Figure 3B; Table 4, "Cocaine script + baseline during stress > Cocaine script + baseline during no stress").

For the stress condition, response to the cocaine script (late) compared to the neutral script (late) indicated activation of the left insula (Figure 3C; Table 4, "Late cocaine > Late neutral during stress"). Neither insular activation nor any other activation was observed when the cocaine and neutral scripts were compared in the no-stress condition.

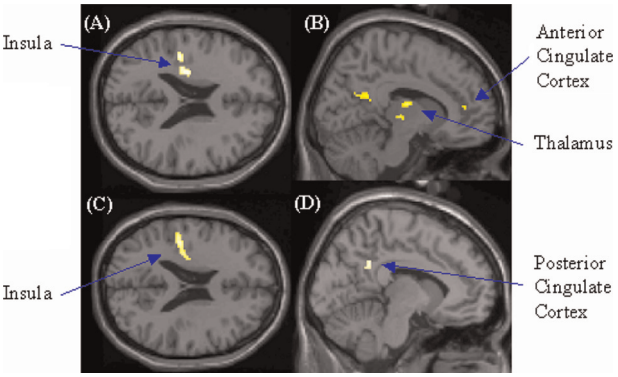

FIGURE 3. BOLD Responses to Cocaine Cue and Stress Condition. (A) Drug-Cue Induced Activation of the Insula During Cocaine Compared to Neutral Scripts (z = 3.10). Response to Early and Late Neutral Scripts were Subtracted from Early and Late Cocaine Scripts with Responses Pooled Across the Stress and No Stress Conditions. (B) Anterior Cingulate Cortex and Thalamic Activation Related to the Presence of a Stressor During Cue-Induced Craving (z = 2.69 and 3.15, respectively). Cocaine Script with No Stress (No Shock Expectation) was Subtracted from Cocaine Script During Stress (Shock Expectation) Conditions. (C) Insula Activation Associated with Cue-Induced Craving During the Stress Condition (z = 3.21). Responses to the Neutral Script During Stress (Shock Expectation) were Subtracted from Cocaine Script During Stress. (D) Posterior Cingulate Activation Associated with Cue-Induced Craving in the Presence of a Stressor (z = 2.70). Interaction Analysis: Script Type (Cocaine > Neutral) by Stressor Condition (Shock > No Shock)

Interaction Analysis of Script Content and Stressor Condition

An interaction analysis between script content and stress condition was conducted using the following model:

$$[\text{Cocaine script} > \text{Neutral script}] \times [\text{Stress condition} > \text{No-Stress condition}].$$

For the analysis conducted on the early components of all four scripts, there were significant interaction effects in the posterior cingulate cortex (Figure 3D) and right parietal lobe, with greater activation during the cocaine script in the presence of the stressor, as seen in Table 5, "(Early cocaine script > Early neutral script) × (Stress > No stress)." Parallel analyses using the late components of the four scripts and using the early plus late components of the four scripts revealed interaction effects for activations in the parietal lobes (see Table 5).

TABLE 4. Effect of a stressor (shock expectation) on cocaine cue-related neural activations

Contrast	Area description	Broadmann's area	Number of voxels	T value	MNI coordinates* x, y, z
Early + late cocaine script during stress > Early + late cocaine script during no stress	Thalamus (R)		26	2.97	12, −12, 14
	Precuneus		229	3.30	−14, −52, 34
Cocaine script + baseline during stress > Cocaine script + baseline during no stress	Anterior cingulate (Figure 3B)	10	6	2.69	12, 42, 12
	Thalamus (R, Figure 3B)		47	3.16	12, −12, 14
	Precuneus		1005	3.83	−14, −52, 34
Neutral and cocaine scripts during stress > Neutral and cocaine scripts during no stress	Thalamus		28	3.16	16, −18, 2
	Precuneus		294	3.71	−18, −54, 34
Neutral scripts during stress > Neutral scripts during no stress	No suprathreshold activations				
Late cocaine > Late neutral during stress condition	Insula (Figure 3C)	13	120	3.28	−41, −24, 22

*Distance (in millimeters) from the midsagittal plane (x coordinates, negative values refer to effects in the left hemisphere), anterior/posterior to the anterior commissure (y coordinates), and superior/inferior to the anterior/posterior commissure plane (z coordinates).

DISCUSSION

Results of this study indicate that exposure to cocaine cues compared to neutral cues resulted in significant activations of posterior cingulate cortex, left insula, and right thalamus in treatment-seeking cocaine-dependent men in an early stage of cocaine abstinence. The experience of cocaine use reminders (ie, guided imagery of personalized cocaine use scripts) during a stress condition (ie, expectation of mild electric shock) was associated with activation of the left insula and anterior cingulate cortex, paralimbic brain areas associated in prior studies with conditioned cocaine craving.

Although we observed areas of activation in response to cocaine cues that are associated with reward processing (insula, anterior and posterior cingulate cortex), other

TABLE 5. Interaction effect of script type (cocaine/neutral) by stressor condition (shock/no shock)

Contrast	Area description	Broadmann's area	Number of voxels	T value	MNI coordinates* x, y, z
(Early cocaine script > Early neutral script) × (Stress > No stress)	Posterior cingulate (Figure 3D)	31	20	2.00	−10, −50, 30
(Late cocaine > Late neutral) × (Stress > No stress)	Parietal lobe, angular gyrus	39	35	2.93	48, −64, 34
	Parietal lobe	40	48	3.13	58, −26, 30
	Inferior parietal lobule (R)		10	2.80	38, −28, 26
(Both cocaine scripts > Both neutral scripts) × (Stress > No stress)	Inferior parietal lobule	40	6	2.66	58, −28, 30
	Parietal lobe, angular gyrus	39	4	2.64	40, −62, 34

*Distance (in millimeters) from the midsagittal plane (x coordinates, negative values refer to effects in the left hemisphere), anterior/posterior to the anterior commissure (y coordinates), and superior/inferior to the anterior/posterior commissure plane (z coordinates).

areas were notably absent, such as the nucleus accumbens, prefrontal cortex, and orbitofrontal cortex. This could be due to the only modest levels of craving our participants attained during scanning, and to the probability that the pathological motivation for drug use involves processes other than incentive and reward processing.

There are several limitations of this study design that deserve mention. Although cocaine craving elicited by the cocaine scripts was greater than craving during the neutral scripts, it was modest in intensity compared to some previous studies.[11–17,33,34] The cocaine craving during the stressor was greater than craving without the stressor, but not significantly so. The modest craving elicited by our paradigm may be related to the distraction posed by the fMRI environment that would impede mental imagery and attentional control related to the auditory scripts used here as cues. Prior work using personalized script-guided imagery for provoking cocaine craving was conducted with PET scanning that affords a quieter, less confined context.[15,17] Another potential cause of the overall modest craving in our participants may be related to their individually varying capacity for mental imagery. Although the mean on the QMI was 59.4 ± 30.8, one participant scored 116, indicating a limited capacity for imagery. This participant rated his craving as "0" during all time points of the fMRI paradigm, although on exit interview after the session, he admitted informally that the scripts did make him want cocaine. In this context, Wang et al.[33] report cardiovascular activations during cocaine-related interviews even in participants who did not report increased craving. Because all of our participants were in early treatment at the time of scanning, they may have wanted to minimize craving reports in the service of believing or having us believe that they were recovering. Another important caveat is that our analyses were conducted using fixed effects models. Therefore, the generalizability of our results to the cocaine-dependent population must remain limited. Studies with greater numbers of participants and using random effects models are needed to confirm the findings of this exploratory study.

Contrary to our hypotheses, we did not see activations of the extended amygdala during the stressor as we had expected. This could be due to the relatively mild stressor (expectation of mild wrist shock) that we used. The fMRI study of Li et al.[22] likewise did not detect amygdala activations in cocaine-dependent subjects during stress imagery. Studies by Phelps et al.[18,19] detected amygdala activation during threat of shock, but these studies used a fear potentiation paradigm in which the threat periods were shorter[18] (18 seconds) and much more numerous. Amygdala activations in response to fearful stimuli are short-lived;[19] hence, the Phelps studies were more optimally designed to detect neural activations related to fear. However, the Phelps study[18] detected insula and anterior cingulate activation during periods of anticipation of shock. These areas were likewise activated in our study during shock expectation.

There were several regions of prominent activation elicited by our paradigm. The insular cortex was activated during cocaine scripts compared to neutral scripts. Activations in this area have been reported during cocaine craving paradigms[14,15,33] and in response to acute cocaine administration.[35,36] In the Wang study,[33] right insular activation was correlated with cocaine craving scores elicited during a cocaine theme interview. The insular cortex has extensive connection with limbic and paralimbic areas, including orbitofrontal cortex, cingulate cortex, amygdala, hypothalamus, and hippocampus.[37–42] The functioning of this area is thought to involve the integration of internal somatic states associated with emotions.[43,44]

Our paradigm elicited the activation of the anterior cingulate cortex during cocaine cue imagery and when shock expectation was compared to no-shock expectation. Anterior cingulate activations have been seen in many of the prior cocaine craving studies.[12–14,16,17,36] Notably, this area was also activated with stress imagery in the paper by Li et al.[22] and is considered part of the limbic brain that is extensively connected to the amygdala.[45] Cognitive functions are attributed to its dorsal portion, whereas its rostral and ventral aspects are more related to emotions.[46] The anterior cingulate functions in the evaluation of incentive cues and in decision making regarding reward.[17,47–49] Posner and Rothbart[50] hypothesize that this region mediates executive control over emotional states. The cocaine cue-related activation of the dorsal anterior cingulate cortex may similarly reflect a cognitive control response that modulates the valuation of cocaine cues.[17]

We also detected posterior cingulate cortex activation during cocaine script imagery and when comparing the stress condition to the no-stress condition. This area was activated during cocaine craving in prior studies by Garavan et al.[14] and Kilts et al.[17] Although the posterior cingulate does not appear to be directly connected with the amygdala,[51] it receives inputs from the anterior cingulate and orbital frontal cortex and sends efferents to the parahippocampal and entorhinal cortices.[52] This area is postulated to mediate the retrieval of autobiographical memories[53] and the processing of incentive salience.[54] In the study of Kilts et al.,[17] the posterior cingulate was activated when cocaine imagery was contrasted with anger imagery, leading to the authors' speculation that this area was specifically associated with reward processing rather than with more generalized emotion processing or autobiographical memory recall.

The activation of areas of the parietal cortex emerged in the interaction analysis, indicating that these areas were engaged selectively in response to conditioned cocaine cues during stress. Although infrequently reported, parietal cortex activation has been observed

during exposure to conditioned cocaine cues.[11,14] The parietal lobe is thought to participate in processing working memory,[55] visuospatial attention,[56] and episodic memory retrieval.[57,58] In a similar vein, the activation of the precuneus emerged when cocaine script imagery during the shock condition was compared to cocaine script imagery during the no-shock condition. This area also has been linked to episodic memory retrieval and the recall of autobiographical memories.[57] The parietal and posterior cingulate cortex activations identified in this interaction analysis suggest that concurrent stress enhances the attentional bias and mnemonic responses to drug use reminders in drug-addicted individuals.

There is considerable overlap and interconnection between brain areas mediating stimulus reinforcement and areas mediating the stress response. Preclinical and clinical studies have elucidated the importance of the mesocorticolimbic dopamine system for the rewarding and incentive motivation properties of drugs of abuse.[6] The reward circuit, encompassing the concept of the extended amygdala, contains the nucleus accumbens, bed nucleus of the stria terminalis (BNST), and central nucleus of the amygdala in an interconnected functional loop. The cortico-thalamo-striatal loop[59] and its connections with the orbitofrontal cortex, dorsolateral prefrontal cortex, and cingulate cortex are hypothesized to mediate dysregulation in the reward circuit in the addicted state.[6] The brain corticotropin releasing factor (CRF) stress system is interconnected with the above reward circuitry, and both are modulated by dopamine.[6,60] The thalamic activations observed during cocaine script imagery with stress compared to cocaine script imagery without stress may represent increased activity in this cortico-thalamo-striatal loop in the face of shock expectation. Although thalamic activation is not typically reported in studies of craving induction, thalamic activation during methylphenidate administration to cocaine abusers was reported in the study by Volkow et al.[61]

In summary, cocaine craving provoked by cocaine cues (cocaine-related personalized scripts) was associated with activation of brain areas associated with reward processing. The presence of a stressor (ie, expectation of mild electric shock) enhanced the cocaine cue-induced activation of brain areas associated with reward processing, as well as those involved in the attentional bias and memory recall properties of conditioned drug cues. This activation of motivation, attention, and memory circuitry may indicate mechanisms by which stress increases vulnerability to cocaine relapse in the face of cocaine cues.

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