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Effects of childhood maltreatment on the neural correlates of stress- and drug cue-induced cocaine craving

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Abstract

Childhood adversity negatively influences all stages of the addiction process and is associated with persistent alterations in neuroendocrine, autonomic and brain responses to stress. We sought to characterize the impact of childhood abuse and neglect on the neural correlates of stress- and drug cue-induced drug craving associated with cocaine addiction. Cocaine-dependent men with (n=20) and without (n=18) moderate to severe childhood maltreatment histories underwent fMRI during script-guided mental imagery of personalized stress, drug use, and neutral experiences. Compared to the neutral script, the stress and drug use scripts activated striatal, prefrontal, posterior cingulate, temporal and cerebellar regions consistent with prior studies of induced states of stress and drug craving. For the stress script, maltreated men exhibited reduced activation of the anterior precuneus and supplementary motor area (SMA); the interaction of maltreatment severity and stress-induced craving responses predicted lesser rostral anterior cingulate cortex activation. For the drug use script, maltreated men exhibited greater left dorsolateral prefrontal cortex activation. The interaction of maltreatment severity and craving responses was associated with greater activation of the visual cortex and SMA, whereas a maltreatment-by-anxiety interaction effect included lesser ventromedial prefrontal cortex activation. The outcomes indicate an association of childhood maltreatment with a heightened appetitive anticipatory response to drug cues and a diminished engagement of regulatory and controlled action selection processes in response to stress- or drug cue-induced drug craving and anxiety responses for cocaine-dependent men. These findings provide novel insights into possible brain mechanisms by which childhood maltreatment heightens risk for relapse in drug-dependent individuals.

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Author Contributions

CK was responsible for the study concept and design. AE, SS and JY performed subject assessments and assisted with script construction. AE performed the data analyses. AE and CK drafted the manuscript. SS and JY provided critical revision of the manuscript for important intellectual content. All authors critically reviewed content and approved final version for publication.

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Keywords

addiction; childhood maltreatment; cocaine; drug cues; fMRI; stress

INTRODUCTION

Cocaine addiction is a chronically relapsing disorder. Relapse to drug use is frequently attributed to drug craving, or the intense desire to consume drugs (Paliwal et al., 2008), and may be precipitated by exposure to the drug itself (De Wit, 1996), exposure to conditioned drug use reminders (Kosten et al., 2005), or exposure to stressors (Sinha, 2007). The clinical relevance of drug craving is supported by the demonstration that the neural correlates of cue-induced drug craving were associated with treatment outcomes in cocaine-dependent patients (Kosten et al., 2005). Subjective anxiety ratings, craving ratings, and neuroendocrine and physiological stress responses to laboratory stressors and drug cues also predict drug use outcomes following treatment for cocaine dependence (Back et al., 2010; Sinha et al., 2006).

Childhood abuse and neglect histories, prevalent among adults with drug use disorders (Dube et al., 2003; Pirard et al., 2005), are associated with persistent alterations in the hypothalamic-pituitary-adrenal (HPA) axis and autonomic nervous system responses to stressors (DeSantis et al., 2011; Heim et al., 2000). Additionally, childhood adversity negatively influences all stages of the addiction process including the initiation of use of drugs of abuse, the transition to compulsive drug use that defines the development of addiction, and the long-term maintenance of the addicted state (Dube et al., 2003; Enoch, 2011). Furthermore, histories of childhood maltreatment negatively impact relapse outcomes (Hyman et al., 2008; Sacks et al., 2008). Therefore, characterization of the effect of childhood maltreatment on the neural correlates of drug craving and stress responses elicited by stressors or drug use reminders may better define the determinants of relapse and potentially reveal important targets of addiction therapies for drug-dependent victims of childhood traumatic experiences. However, studies of craving and anxiety responses to stressors and drug cues have yet to investigate the contribution of childhood adversity.

Script-guided mental imagery of personalized drug use and stressful situations is a laboratory technique of proven value to study and compare craving responses in drug-dependent individuals (Kilts et al., 2004; Kilts et al., 2001; Potenza et al., 2012; Sinha et al., 2005). Previous human functional neuroimaging studies of script-guided mental imagery responses suggest the involvement of a network of limbic, paralimbic, striatal, medial frontal and orbitofrontal brain regions in mediating conditioned drug cue-induced craving (Kilts et al., 2001; Potenza et al., 2012), which differs for men and women (Kilts et al., 2004). Similarly, fMRI studies of script-guided mental imagery of personalized stressful experiences indicate stress-induced cocaine craving is associated with sex-dependent activation of the hippocampus, insula, striatum, and dorsomedial, ventromedial and dorsolateral prefrontal cortex (Li et al., 2005; Potenza et al., 2012; Sinha, 2007; Sinha et al., 2005; Sinha et al., 2007).

This study sought to extend previous neuroimaging studies of the mechanisms of relapse to drug seeking and use behaviors in cocaine-dependent individuals by investigating the impact of childhood maltreatment histories on the neural correlates of stress- and drug cue-induced craving and anxiety. We hypothesized that the association of childhood maltreatment with a more negative clinical course of drug use disorders is reflected in alterations in the neural correlates of cocaine craving and anxiety elicited by stressors and drug use reminders. A further hypothesis was that the pattern of neural processing of drug and stress cues determines the variation in drug craving responses. Thirty-nine cocaine-dependent men underwent fMRI during mental imagery of a neutral script, a personalized drug use script, and a personalized script of a stressful experience.

METHODS

Subjects

Twenty cocaine-dependent men with significant exposure to childhood abuse or neglect [40.5 ± 7.8 (mean ± standard deviation) years of age] and eighteen cocaine-dependent men with minimal exposure to childhood abuse or neglect (41.0 ± 7.1 years of age) were enrolled in the study. This study focused on an all-male sample of cocaine-dependent individuals due to known sex differences in the neural correlates of drug cue- and stress-induced craving (Kilts et al., 2001; Potenza et al., 2012). Subjects were current cocaine users who were neither treatment-seeking nor treatment-engaged and were recruited through responses to local newspaper advertisements, Little Rock city bus advertisements, or flyers posted in the community. During the first study visit subjects were evaluated for study eligibility, completed questionnaires and developed personalized scripts for use in the second, fMRI visit. Urinalyses conducted the day of the fMRI visit detected recent use of cocaine or other drugs of abuse.

Inclusion/exclusion criteria

Cocaine-dependent men between the ages of 18–50 were eligible to participate. Cocaine dependence was assessed using the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I) (First et al., 2007). Dependence or abuse of other drugs with the exception of alcohol, nicotine or marijuana were exclusion criteria. Other current or past Axis I disorders as determined by SCID interview were exclusion criteria except for past mood or anxiety disorders. Subjects with a history of loss of consciousness greater than 10 minutes, significant sensory impairment, major medical disorders, use of psychoactive medication within the past 30 days, or uncontrolled hypertension or diabetes were excluded. After a full explanation of study procedures approved by the Institutional Review Board of the University of Arkansas for Medical Sciences (UAMS), eligible subjects provided written informed consent to participate.

Childhood maltreatment assessment

Initial study eligibility and childhood maltreatment status were assessed using a telephone screening instrument. Subjects were designated as having or not having experienced significant childhood maltreatment using previously established questions and criteria (Heim et al., 2000; Vythilingam et al., 2002) selected from the Early Trauma Inventory (Bremner et

al., 2000). Specifically, childhood maltreatment group assignments were based on responses to nine questions indicating frequencies of at least one form of maltreatment (sexual, physical, and emotional abuse and neglect) greater than once per year and before the age of 13, in accordance with evidence that early and repeated exposures to maltreatment are particularly associated with negative later life outcomes (Lupien et al., 2009). This group assignment was retained in further assessment and data analysis. Sexual abuse included experience of unwanted attempted or successful sex or touching of sexual organs. Physical abuse was defined as being hit, kicked or beaten by an older person (non-peer). Physical neglect was defined as the denial of adequate sustenance and shelter. Emotional abuse or neglect included being ridiculed or ignored.

During the first study visit, childhood maltreatment histories were quantitatively assessed with the 28-item Childhood Trauma Questionnaire (CTQ; Bernstein et al., 2003), providing measures of childhood exposure to physical, emotional and sexual abuse and physical and emotional neglect. Scores for each maltreatment type range from 5–25, and potential CTQ total scores range from 25–125, exposing a dynamic range of trauma experiences across both maltreated and non-maltreated men. The CTQ demonstrates good internal consistency, classification accuracy, and validity for drug-abusing individuals (Bernstein et al., 2003; Thombs et al., 2007). Different types of maltreatment tend to be correlated, and maltreatment subscales of the CTQ load onto a higher-order factor (Scher et al., 2001). Thus, primary data analyses in this study used the CTQ total score to provide a cumulative measure of maltreatment.

Script generation

Subjects selected a neutral script from a set of four paragraphs describing nature scenes (beach, forest, lake, river) in the first person, present tense similar to previous guided-imagery studies of induced cocaine craving (Kilts et al., 2004; Kilts et al., 2001; Potenza et al., 2012). Subjects were instructed that they should be able to relate to the scene through previous experience. Study staff transcribed or assisted subjects in writing two additional scripts. One script detailed a stressful experience unrelated to drug use. A second described personal events leading to cocaine use that depicted a typical cocaine use experience and was not particularly stressful. All three scripts included details regarding sensory (i.e. sights, sounds, smells) and physiological sensations experienced (see Figure S1 for representative examples). For the stress and cocaine scripts, subjects selected physiological sensations from a list of 33 words or phrases (*e.g.* “heart races,” “gasping for air,” “jittery”) for incorporation into the final, edited script. Scripts were read aloud by a female voice in the first person, present tense, recorded in audio format, and edited to one minute in length.

fMRI procedures

Subjects were scanned with a Philips Achieva 3T MRI system and 8-channel head coil (Philips Healthcare, USA) at the Brain Imaging Research Center (BIRC) at UAMS. Functional T2* Echo Planar Images were acquired with the following parameters: 3×3×3 mm^3 voxels, 34 slices, TR=2000 ms, TE=30 ms, FOV=192×192 mm^2, flip angle (FA)=90°, matrix=64×64. Anatomical images were acquired for functional image registration and

tissue segmentation purposes using a T1 MPRAGE sequence (matrix=256×256, 160 slices, TR=2600 ms, TE=3.02 ms, FA=8°, final resolution=1×1×1 mm^3).

The scanning session began with a 62.5 second continuous performance task (CPT) in which alphabetical letters appeared in the center of a screen every 0.5 seconds and subjects were instructed to respond with a button press whenever the letter X was preceded by the letter A. The CPT was followed by a 60 second rest period during which a visual fixation cross was displayed. The neutral script was presented in audio format through headphones and combined with the visual display of the words on the screen. A subsequent two minute mental imagery period consisted of a fixation cross on the screen with prior instructions to continue to imagine the event described in the script. The imagery period was followed by a rating period during which subjects indicated, using a button box, their anxiety level, cocaine craving level, and the vividness of the mental image on a scale of 0–10. Starting with the CPT as a between-script distracter, these procedures were repeated for the personalized stress and cocaine use scripts, with the order of the latter two scripts counterbalanced across subjects.

fMRI data preprocessing

fMRI data were preprocessed with Analysis of Functional Neuroimages software (AFNI) (Cox, 1996) using the following steps: slice time correction, deobliquing, motion correction, despiking, alignment to the subject's anatomical image, warping to MNI standardized space, Gaussian smoothing at 6 mm full width at half maximum, scaling to percent signal change, removal of independent components for which the spatial maps correlated with "striping" artifacts or for which the time courses were highly correlated with principal components derived from signal in white matter and cerebral spinal fluid voxel time courses.

Data analysis

The effects of script condition, maltreatment and their interaction on craving, anxiety and imagery ratings were assessed by two-way repeated measures analysis of variance.

Single subject fMRI data were analyzed using restricted maximum likelihood estimation of sustained increases or decreases in voxel activation (modeled as blocks) during script presentation and imagery periods relative to rest periods with 3dDeconvolve and 3dREMLfit in AFNI. A stress versus neutral script condition contrast was defined by the estimates of the stress script presentation and imagery period minus the neutral script presentation and imagery period. The contrast of the cocaine versus neutral script conditions was defined by the estimates of the cocaine script presentation and imagery period minus the neutral script presentation and imagery period. The script presentation and imagery conditions were modeled separately at the individual subject level but pooled in the contrasts due to our prior observation that script presentation was often a stimulus for simultaneous mental imagery in cocaine-dependent individuals. The main effect of the neutral imagery condition was also modeled in a one sample test by contrast to the resting baseline condition. The CPT blocks were also modeled, but analysis of their brain-behavior relationships was beyond the scope of the current analysis.

Group-level mixed-effects meta-analyses were performed in AFNI using 3dMEMA to identify, using data from all 38 subjects, those voxels that were associated with the stress-neutral, cocaine-neutral, and neutral-baseline contrasts. To assess the effects of childhood maltreatment on each of these contrasts, two levels of analyses modeled maltreatment as a categorical variable in group comparisons and as a continuous variable using CTQ scores in interaction analyses in the total participant sample. The maltreated versus non-maltreated group comparison of the stress-neutral, cocaine-neutral, and neutral-baseline conditions was conducted in 3dMEMA. To control for the influence of the variable of frequency of recent cocaine use, group comparisons modeled the reported past 30 day cocaine use (n days) as a covariate.

To test the primary study hypothesis that childhood maltreatment modifies the neural correlates of stress- and drug-cue-induced craving and anxiety, the interaction of CTQ scores and in-scanner craving/anxiety self-ratings regressed on the stress-neutral and cocaine-neutral contrasts were tested (one sample) in 3dMEMA. To control for the influence of the variable of level of recent cocaine use, all interaction effect analyses also modeled the reported past 30 day cocaine use as a covariate. All group-level results were cluster-level corrected for multiple comparisons ($p<0.005$, 24 contiguous voxels) based on 10,000 Monte Carlo simulations conducted in AFNI's 3dClustSim, providing a corrected significance level of $p<0.05$.

The study groups differed in exposure to the three subtypes of childhood abuse, but not for neglect subtypes. The association of individual CTQ subscale scores for physical, emotional and sexual abuse with effects on the neural correlates of stress- and drug cue-induced craving and anxiety were assessed in post-hoc analysis. Regions-of-interest (ROI) were defined as all significant voxels within each cluster identified in group categorical and interaction analyses. For each ROI, the mean estimate of voxels in the contrast from which the ROI was defined was calculated for each subject. Next, these values were each entered as a dependent variable in general linear model to test the effects of each CTQ subscale (for ROI defined by categorical group comparisons) or CTQ subscale-by-rating interaction (for ROI defined by CTQ total score interaction analyses).

RESULTS

Subject demographic and clinical variables are reported by maltreatment group in Table 1. Consistent with the high prevalence of childhood maltreatment in drug-dependent individuals (Dube et al., 2003; Pirard et al., 2005), the mean CTQ total score for the entire sample was 49.9 (median: 47, standard deviation: 17.9 range: 28–106). Compared with the non-maltreated men, the maltreated group reported significantly higher CTQ total scores and CTQ subscale scores for physical abuse, emotional abuse, and sexual abuse (Table 1). The CTQ total scores for the non-maltreated group approach the 90^{th} percentile value of 41 for a community male sample (Scher et al., 2001). The two groups did not significantly differ in childhood physical or emotional neglect, age, education, race or ethnicity, recent or lifetime cocaine use, alcohol use disorders, frequency of cigarette use, past major depressive disorder (current diagnosis was excluded), DSM-!V symptoms of ADHD, or prevalence of cocaine-positive urinalysis results the day of the fMRI (Table 1). Of the cocaine-positive

participants, two in each group were also positive for THC and one in the maltreated group was positive for THC and methamphetamine. Of the cocaine-negative participants two belonging to the maltreated group also tested positive for THC.

Drug craving and anxiety responses to script-guided mental imagery

Drug craving, anxiety, and imagery response ratings related to script-guided mental imagery are reported in Table 1. Craving and anxiety rating responses are depicted by maltreatment status and script condition in Figure 1. All script conditions were associated with a high degree of inter-individual variability in drug craving and anxiety ratings (Figure 1), consistent with a wide range of baseline drug craving and anxiety. For the entire sample, the average reported urge to use cocaine increased from 4.0 ± 2.7 for the neutral script to 5.0 ± 2.9 for the drug script and 5.0 ± 3.0 for the stress script. The average anxiety rating increased from 3.1 ± 2.7 to 3.9 ± 2.8 for the drug script and 4.3 ± 3.2 for the stress script. However, the effect of script condition did not meet statistical significance for cocaine craving ($F(2,111)=1.68$, $p=0.19$) or anxiety response ($F(2,111)=1.83$, $p=0.17$) ratings. There was a significant effect of script condition on subjects' ratings of the vividness of the mental image ($F(2,111)=18.65$, $p<0.001$), where both the cocaine and stress script conditions produced significantly greater ratings of vividness of the related mental image compared to the neutral script condition. There was no significant effect of maltreatment status or its interaction with script condition on subjects' ratings of vividness, drug craving or anxiety.

To explore the potential sources of variability observed in self-reported craving and anxiety ratings, we conducted secondary analyses based on evidence that frequency of recent cocaine use is associated with anxiety and craving responses to script-guided mental imagery of personalized stress and drug use situations (Fox et al., 2005). Indeed, the reported number of days of cocaine use in the past 30 days was positively correlated with cocaine craving ratings in response to both the cocaine script ($r=0.41$, $p=0.012$) and the stress script ($r=0.38$, $p=0.018$); there was no effect of maltreatment group on this association. In contrast, a cocaine use-by-maltreatment group interaction indicated that level of cocaine use in the past 30 days predicted greater anxiety responses for the cocaine script in maltreated men but lesser responses in non-maltreated men ($t=-2.36$, $p=0.024$). A similar relationship was also identified for the stress script ($t=-2.44$, $p=0.021$).

fMRI response to script-guided mental imagery

Stress-Neutral script—Brain regions demonstrating significantly elevated activity ($p<0.05$, corrected) for the stress-neutral condition contrast included the dorsomedial prefrontal cortex, left inferior frontal gyrus (pars triangularis), posterior cingulate cortex/precuneus, left anterior superior temporal sulcus, and right cerebellum. Relative decreases in activity for the stress script were identified in the right occipital-temporal junction (Table 2).

Drug-Neutral script—Significant clusters of activation ($p<0.05$, corrected) for the cocaine-neutral contrast are reported in Table 3. Greater activation was observed for the cocaine-neutral contrast in the right ventral striatum, subgenual cingulate cortex, posterior cingulate cortex/precuneus/cuneus, right cerebellum and dorsomedial prefrontal cortex.

Neutral script – resting baseline—Relative to the resting state baseline, neutral script imagery was associated with significant activation ($p<0.05$, corrected) of the cuneus, cerebellum, inferior frontal cortex (pars triangularis) and left superior parietal cortex and right angular gyrus. Relative decreases in activity were observed in the ventromedial prefrontal cortex, lingual gyrus, bilateral somatosensory cortex and precuneus, and right insula (Table S1). There was no significant effect of maltreatment group on the neural response to the neutral script for its contrast to the baseline condition.

fMRI response and effect of childhood maltreatment

Stress-Neutral script—The comparison of maltreated versus non-maltreated men indicated less activity in the left dorsal-anterior precuneus and left SMA/pre-SMA in maltreated men for the stress-neutral contrast (Table 2). The interaction of CTQ total scores and self-rated craving responses to stress script imagery significantly predicted greater activity in the left premotor cortex and right cerebellum, and lesser activity in the rostral anterior cingulate cortex (Table 2; Figure 2A). The interaction of CTQ total scores and stress script-related anxiety responses predicted increased activity in the left motor cortex and thalamus (Table 2; Figure 2B).

Drug-Neutral script—The comparison of maltreated versus non-maltreated men indicated greater activity in the left middle frontal gyrus (Brodmann area 10) in maltreated men for the drug-neutral contrast (Table 3). The interaction of CTQ total scores and craving responses during cocaine script imagery was associated with greater activation in bilateral occipital cortex, caudal pre-SMA, and cuneus, and lesser activity in the right posterior parietal cortex (Table 3; Figure 2C). The CTQ total score-by-anxiety rating interaction predicted lesser activity in the ventromedial prefrontal cortex and right lingual gyrus for the cocaine-neutral contrast (Table 3; Figure 2D).

Post-hoc tests of CTQ subscale effects—Detailed results of post-hoc tests of the effects of subtypes of childhood maltreatment for the three abuse-related CTQ subscales that differed between the groups are presented in Table 4. Generally, regions defined by the categorical effects of maltreatment (i.e. left middle frontal gyrus for the cocaine versus neutral script condition and the left precuneus and supplementary motor area for the stress versus neutral script condition), were most strongly associated with the experiences of physical abuse and emotional abuse, but not sexual abuse, a finding consistent with large differences in the prevalence of these forms of maltreatment between the groups. ROIs defined by cocaine script rating interactions exhibited significant interaction effects for the emotional abuse subscale (i.e., craving interaction: right middle occipital gyrus; anxiety interaction: medial frontal gyrus and right lingual gyrus) and sexual abuse subscale (i.e. anxiety interaction: right lingual gyrus). On the other hand, none of the ROIs for the stress script rating x CTQ subscale scores exhibited significant interaction effects (Table 4). The latter interaction effects may thus reflect cumulative exposure to multiple types of childhood maltreatment.

DISCUSSION

The present study sought to identify the influence of childhood abuse and neglect on the brain response to stress and drug cues in drug-dependent men. The brain responses to script-guided mental imagery of drug use and stressful experiences were significantly altered by a history of childhood maltreatment. In particular, childhood maltreatment altered the neural correlates of drug craving and anxiety, indicating potential maladaptive neural responses to two major recognized precipitants of relapse in cocaine dependent men with maltreatment histories. Overall, an ROI analysis of the effects of childhood abuse subtypes supported a particularly significant impact of emotional abuse. Also, as the level of recent cocaine use significantly influenced craving and stress responses to the mental imagery conditions, the level of past 30 day cocaine use was modeled as a continuous explanatory variable in the fMRI analysis of neural responses to script imagery.

Similar to prior studies (Li et al., 2005; Sinha et al., 2005), stress-induced drug craving was associated with activation of the dorsomedial prefrontal cortex, posterior cingulate cortex, left inferior frontal gyrus, and superior temporal sulcus. The observation that childhood maltreatment history diminished both the dorsal-anterior precuneus and pre-SMA/SMA responses to stress suggests a functional compromise in the ability to engage parietal-motor networks (Zhang and Li, 2012) related to attentional (Nachev et al., 2008), behavioral (Zhang and Li, 2010), and emotion (Kohn et al., 2014) regulation, and controlled versus automated action selection (Nachev et al., 2008) in response to stressful experiences. Group differences in emotional and physical abuse disproportionately contributed to the effect of maltreatment on the pre-SMA/SMA and precuneus stress responses. These two subtypes of childhood abuse are highly correlated although emotional abuse represents a stronger predictor of adult personality pathology (Cohen et al., 2013). When activated by stressors, the processes of drug seeking and use behaviors are proposed to be automatically engaged (Vanderschuren and Pierce, 2010). Further research needs to address specifically whether such a compromise in the volitional control of behavior underlies the link between childhood adversity and heightened risk for relapse in drug-dependent individuals. The contention that impulsivity represents an intermediate mechanism in a pathway from childhood adversity to adult drug addiction (Hosking and Winstanley, 2011) is consistent with this association.

Activity within the rostral anterior cingulate cortex, negatively predicted by the interaction between severity of childhood maltreatment and the stress-induced craving response, is involved in resolving emotional conflict (Etkin et al., 2006). This interaction effect suggests that childhood maltreatment disables a key mechanism of conflict resolution responsible for adaptive responses to stress, and does so in a graded manner dependent on the severity of experienced maltreatment. This possibility is consistent with observed persistent increases in autonomic and neuroendocrine responses to stress for adults exposed to childhood maltreatment (Heim et al., 2000; Heim et al., 2008).

Similar to prior studies (Chase et al., 2011; Kilts et al., 2001), drug cue-induced craving was associated with activation of the striatum, posterior cingulate cortex, and cerebellum. Childhood maltreatment was associated with significantly enhanced drug cue-related

activation of left anterior dorsolateral prefrontal cortex. Increasing severity of childhood physical or emotional, but not sexual abuse, was associated with increased drug cue-related activation in this region. Increased activity in a similar region was identified in drug-dependent individuals anticipating the opportunity to use drugs in response to drug use cues (Wilson et al., 2012; x=−23, y=61, z=16, BA 10), which was proposed to reflect planning-related integration of motivational states with information regarding drug availability (McBride et al., 2006; Wilson et al., 2004). Evidence from repetitive transcranial magnetic stimulation (rTMS) of the left dorsolateral prefrontal cortex further supports a role of this region in regulating the craving and drug use responses to drug cues (Boggio et al., 2008), perhaps by regulating release of dopamine in craving-related brain regions (Cho and Strafella, 2009). Thus, an enhanced engagement of this region by maltreated individuals may reflect the need to employ cognitive mechanisms to reconcile enhanced cocaine motivational states associated with childhood maltreatment exposure with the lack of drug use opportunity in the study environment.

Activity within the bilateral extrastriate cortex was positively associated with the interaction of childhood maltreatment severity and drug cue-induced craving responses. Drug cue-related activation of the occipital cortex is attributed to the modulation of visual attention by the conditioned incentive motivation properties of drug cues (Hogarth et al., 2009). Heightened attentional bias for conditioned drug cues is associated with greater drug craving responses (Field et al., 2009), whereas effortful regulation of craving responses to drug cues dampens occipital cortical responses (Brody et al., 2007). The heightened visual cortex response to conditioned cocaine cues for men with greater childhood maltreatment exposure suggests their elevated incentive motivation leads to enhanced drug craving responses and thus potential to relapse.

Finally, activity within the ventromedial prefrontal cortex (vmPFC) and lingual gyrus were negatively predicted by the interaction between severity of childhood maltreatment and drug cue-induced anxiety responses. Of the childhood abuse subtypes, this effect was most attributable to exposure to emotional abuse. The vmPFC is involved in the top-down control of emotion, by suppressing negative emotion processing in limbic areas (Etkin et al., 2011). The observed interaction effect suggests that childhood maltreatment moderates the brain stress response by limiting the regulation of stress responses to conditioned drug cues. The lingual gyrus represents a component of the ventral stream of visual stimulus processing and is critical to location memory (Greve et al., 2010) and involved in emotion stimulus processing (Kitada et al., 2010). Diminished activity in this region in response to stressful stimuli has been attributed to resilience to risk for psychopathology associated with childhood maltreatment, as has its increased functional connectivity with anterior cingulate cortex representations of the resting state salience network (van der Werff et al., 2013). An interesting, though speculative, inference is that the capacity of lingual gyrus suppression to reduce anxiety responses is diminished in drug-dependent men with more severe trauma histories, potentially moderating relapse risk by impairing their ability to manage stress response to drug cues.

Limitations

The neutral script condition was associated with widely varying baseline drug craving states. Therefore the contrast of stress and drug use script conditions with this state underestimates their drug craving-related neural responses. Additionally, the generalizability of the study findings to cocaine-dependent populations is limited by the study of exclusively males. In fact, recent evidence suggests the association of childhood abuse or neglect with relapse in adults with drug use disorders is more demonstrable in women (Hyman et al., 2008). Future studies assessing the impact of childhood maltreatment on the neural, craving, and anxiety responses to stress and drug cues in cocaine-dependent women are warranted to explore sex differences in relapse liability. The cross-sectional nature of the study design precludes a definitive test of the primary study hypothesis that observed childhood maltreatment-related alterations in drug cue- and stress-related neural responses underlie the recognized association of early life adversity with the initiation, development and maintenance of drug use disorders. A longitudinal design or further cross-sectional comparisons across other subject groups would aid this test. For instance, the present study did not include a sample of non-drug dependent men. However, the focus of the present study was on characterizing the effect of childhood maltreatment on the brain stress and drug craving response, so matched cocaine-dependent samples were deemed to be of first priority for testing the primary study hypothesis. A further perceived study limitation is the exclusive focus on non-treatment seeking drug-dependent individuals as this variable influences the brain-drug craving association (Chase et al., 2011) and limits the meaningful comparison of results with those obtained for treatment-seeking persons (e.g., (Potenza et al., 2012)).

Conclusions

Both childhood maltreatment and chronic cocaine abuse are associated with neuroadaptive responses in stress and behavioral control brain systems that may enhance susceptibility to relapse in drug-dependent individuals. The growing literature characterizing the neural correlates of stress- and drug cue-induced craving is characterized by a lack of consensus and often contradictory findings. A similarly growing number of contextual variables have been identified as contributing to the variability of neuroimaging findings (Wilson et al., 2004, 2012). The results of the present study indicate that childhood maltreatment results in maladaptive neural responses to stress and drug cues, altering their relationship with drug craving. This study therefore reveals possible neurodevelopmental effects of childhood maltreatment that moderate the reported heightened risk for relapse, though future studies are needed to definitively characterize their relative roles. The usually hidden variable of early life adversity represents another, significant contextual variable that contributes to individual differences in the brain-behavior relationships that regulate relapse in drug-dependent individuals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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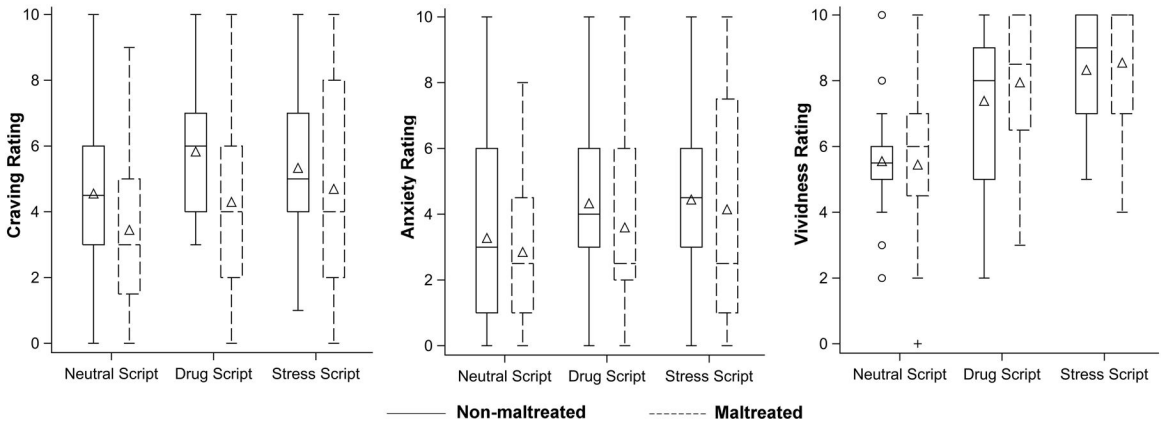

Figure 1.

Box plots illustrating the mean, median, range and outlier responses to script-guided mental imagery for samples of cocaine-dependent men with or without histories of childhood maltreatment.

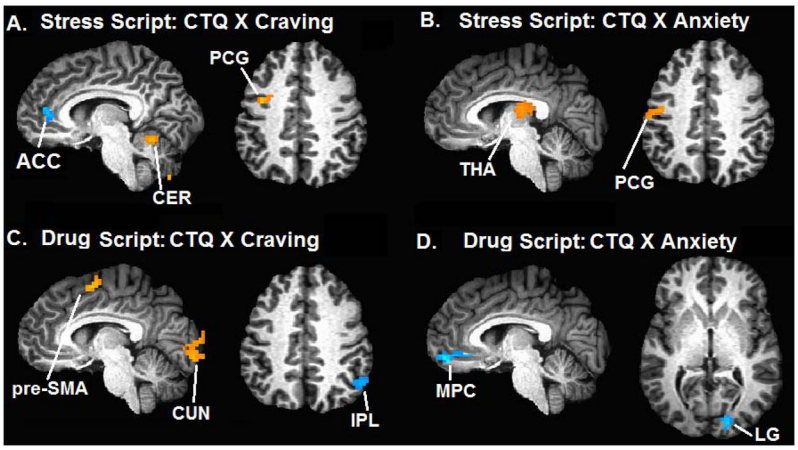

Figure 2.

Neural responses associated with A) the interaction of CTQ total scores and craving responses to stress imagery, B) the interaction of CTQ total scores and anxiety responses to stress imagery, C) the interaction of CTQ total scores and craving responses to cocaine use imagery and D) the interaction of CTQ total scores and anxiety responses to cocaine use imagery.

CER, cerebellum; CUN. cuneus; IPL, inferior parietal lobule; LG, lingual gyrus; MFG, medial prefrontal cortex; PCG, precentral gyrus; pre-SMA, pre-supplementary motor area; THA, thalamus.

Table 1

Demographic and clinical variables, and script-guided imagery responses for the samples of cocaine-dependent men with or without histories of childhood maltreatment

	Non-Maltreated (n=18)	Maltreated (n=20)	
Age (years)	41.0 ± 7.1	40.5 ± 7.8	NS
Education (years)	12.2 ± 1.1	12.7 ± 1.7	NS
Race (black/white)	15/3	17/3	NS
CTQ total score	40.2 ± 10.5	58.5 ± 19.3	t=3.68, p<0.001
Physical abuse	7.8 ± 2.1	12.3 ± 3.8	t=4.58, p<0.001
Emotional abuse	8.3 ± 2.6	12.8 ± 4.2	t=3.87, p<0.001
Sexual abuse	5.5 ± 1.3	9.8 ± 6.5	t=2.86, p=0.01
Physical neglect	7.9 ± 3.7	10.7 ± 5.1	NS
Emotional neglect	10.7 ± 4.5	13.0 ± 6.6	NS
Lifetime cocaine use (years)	13.9 ± 7.3	14.7 ± 8.7	NS
Prior 30 day cocaine use (days)	12.1 ± 8.3	11.6 ± 10.0	NS
Prior 7 day cocaine use (days)	2.4 ± 2.2	2.4 ± 2.3	NS
Positive cocaine urinalysis	14	12	NS
Alcohol abuse (current/lifetime)	2/4	1/4	NS
Alcohol dependence (current/lifetime)	5/10	7/13	NS
Marijuana abuse (current/lifetime)	3/7	0/7	NS
Marijuana dependence (current/lifetime)	3/10	5/8	NS
Cigarette smokers	14	17	NS
Cigarettes per day (among smokers)	13 ± 7	11 ± 6	NS
Major depressive disorder (current/lifetime)	0/5	0/7	NS
CAARS DSM-IV total ADHD symptoms	41.9	49.3	NS
Drug craving rating			
Neutral script	4.6 ± 2.7	3.5 ± 2.6	NS
Drug script	5.8 ± 2.1	4.3 ± 3.3	NS
Stress script	5.3 ± 2.4	4.7 ± 3.5	NS
Anxiety rating			
Neutral script	3.3 ± 3.0	2.9 ± 2.5	NS
Drug script	4.3 ± 2.7	3.6 ± 3.0	NS
Stress script	4.14 ± 2.6	4.2 ± 3.7	NS
Vividness rating			
Neutral script	5.6 ± 1.8	5.5 ± 2.7	NS
Drug script	7.4 ± 2.4	8.0 ± 2.3	NS
Stress script	8.3 ± 1.8	8.6 ± 2.0	NS

Values represent mean ± 1 SD. Drug craving, anxiety, and image vividness ratings reflect responses to 11-point (0–10) Likert scales. CTQ, Childhood Trauma Questionnaire; CAARS, Conners' Adult ADHD Rating Scales; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; ADHD, attention deficit hyperactivity disorder.

Table 2

Main effect of stress imagery (versus neutral), childhood maltreatment, and the interaction of maltreatment severity and drug craving and anxiety responses

Anatomical Region	X	Y	Z	BA	# voxels	t statistic
L medial frontal gyrus	−7.5	58.5	38.5	9	35	5.42
R superior frontal gyrus/pre-SMA	−10.5	19.5	62.5	6	57	4.67
L superior temporal sulcus	−43.5	−25.5	−3.5	21	42	4.43
L inferior frontal gyrus	−55.5	28.5	14.5	45	39	4.42
L superior temporal sulcus	−61.5	−10.5	−6.5	22	50	4.33
R cerebellum	22.5	−67.5	−45.5		52	4.21
L posterior cingulate/precuneus	−10.5	−58.5	26.5	31	53	3.60
R middle temporal gyrus/middle occipital gyrus	46.5	−67.5	5.5	37/39	66	−4.82

Greater activity in non-maltreated versus maltreated men for contrast of stress versus neutral script condition

Anatomical Region	X	Y	Z	BA	# voxels	t statistic
L precuneus	−19.5	−49.5	50.5	7	43	4.97
L SMA/pre-SMA	−10.5	−4.5	59.5	6	38	4.34

Interaction of CTQ scores and craving ratings following stress script

Anatomical Region	X	Y	Z	BA	# voxels	t statistic
L precentral gyrus	−37.5	−4.5	41.5	6	50	4.68
R cerebellum	22.5	−73.5	−48.5		50	4.62
R cerebellum	7.5	−58.5	−12.5		46	3.90
rostral ACC	−1.5	46.5	−0.5	32	60	−4.63

Interaction of CTQ scores and anxiety ratings following stress script

Anatomical Region	X	Y	Z	BA	# voxels	t statistic
L precentral gyrus	−55.5	−16.5	38.5	4	49	4.60
thalamus	1.5	−19.5	20.5	9	104	4.26

Table 3

Main effect of cocaine use imagery (versus neutral), childhood maltreatment, and interaction of maltreatment severity with cocaine craving and anxiety responses

Anatomical Region	X	Y	Z	BA	# voxels	t statistic
R cerebellum	82.5	−25.5	−36.5		42	5.76
L posterior cingulate/precuneus	−10.5	−58.5	26.5	31	64	5.55
R cerebellum	28.5	−61.5	−54.5		134	5.32
R caudate/nucleus accumbens/subgenual cingulate	10.5	13.5	2.5		62	4.81
L superior frontal gyrus	−10.5	25.5	59.5	6	38	4.04

Greater activity in maltreated versus non-maltreated men for contrast of cocaine versus neutral script condition

Anatomical Region	X	Y	Z	BA	# voxels	t statistic
L middle frontal gyrus	−43.5	43.5	11.5	10	42	−3.70

Interaction of CTQ scores and craving ratings following cocaine script

Anatomical Region	X	Y	Z	BA	# voxels	t statistic
L middle occipital gyrus	−34.5	−91.5	2.5	18	73	4.67
L precentral gyrus	−25.5	−22.5	74.5	6	35	4.49
pre-SMA	−7.5	1.5	56.5	6	46	4.35
L cuneus	−4.5	.97.5	2.5	17	175	4.11
R inferior occipital gyrus	37.5	−85.5	−9.5	18	47	3.95
R inferior parietal lobule	52.5	−58.5	44.5	40	44	−3.73

Interaction of CTQ scores and anxiety ratings following cocaine script

Anatomical Region	X	Y	Z	BA	# voxels	t statistic
ventromedial prefrontal cortex	−4.5	52.5	−12.5	11	131	−5.49
R lingual gyrus	16.5	−88.5	2.5	17	41	−4.42

Table 4

Effects of CTQ sub-scores on regions demonstrating greater activity in maltreated versus non-maltreated men for the contrast of cocaine versus neutral script condition

Anatomical Region	CTQ PA		CTQ EA		CTQ SA	
L middle frontal gyrus	**t=3.07**	**p<0.01**	**t=2.20**	**p=0.03**	t=0.98	p=0.33

Interaction of CTQ sub-scores and craving ratings following cocaine script

Anatomical Region	CTQ PA		CTQ EA		CTQ SA	
R middle occipital gyrus	t=−0.89	p=0.38	**t=−2.10**	**p=0.04**	t=−1.21	p=0.23
L precentral gyrus	t=−1.69	p=0.10	t=−1.94	p=0.06	t=−1.48	p=0.15
pre-supplementary motor area	t=0.40	p=0.69	t=−0.26	p=0.79	t=−0.29	p=0.77
L cuneus	t=−1.26	p=0.22	t=−1.21	p=0.23	t=0.16	p=0.88
R inferior occipital gyrus	t=−0.42	p=0.68	t=−1.62	p=0.11	t=−0.37	p=0.71
R inferior parietal lobule	t=0.97	p=0.68	t=0.60	p=0.55	t=0.32	p=0.75

Interaction of CTQ sub-scores and anxiety ratings following cocaine script

Anatomical Region	CTQ PA		CTQ EA		CTQ SA	
medial frontal gyrus	t=−2.03	p=0.05	**t=−2.11**	**p=0.04**	t=−0.61	p=0.55
R lingual gyrus	t=−1.94	p=0.06	**t=−2.63**	**p=0.01**	**t=−2.19**	**p=0.03**

Effects of CTQ sub-scores on regions demonstrating greater activity in non- maltreated versus maltreated men for the contrast of stress versus neutral script condition

Anatomical Region	CTQ PA		CTQ EA		CTQ SA	
L precuneus	t=−1.93	p=0.06	**t=−2.67**	**p=0.01**	t=−1.56	p=0.13
L SMA/pre-SMA	**t=−3.15**	**p<0.01**	**t=−2.8**	**p=0.01**	t=−1.09	p=0.29

Interaction of CTQ sub-scores and craving ratings following stress script

Anatomical Region	CTQ PA		CTQ EA		CTQ SA	
L middle frontal/precentral gyrus	t=−1.46	p=0.15	t=−0.94	p=0.35	t=−0.07	p=0.94
R cerebellum	t=−0.91	p=0.37	t=0.02	p=0.99	t=1.05	p=0.30
R cerebellum	t=−0.87	p=0.39	t=−1.33	p=0.19	t=−1.39	p=0.17
medial frontal gyrus	t=1.66	p=0.11	t=0.96	p=0.34	t=−0.52	p=0.60

Interaction of CTQ sub-scores and anxiety ratings following stress script

Anatomical Region	CTQ PA		CTQ EA		CTQ SA	
L precentral gyrus	t=−1.06	p=0.30	t=−1.41	p=0.17	t=−0.58	p=0.56
thalamus	t=0.56	p=0.58	t=−0.24	p=0.81	t=−0.79	p=0.44

Bold type represents significant effects. CTQ, Childhood Trauma Questionnaire; PA, physical abuse subscale; EA, emotional abuse subscale; SA, sexual abuse subscale.