Emotional, physical and sexual abuse are associated with a heightened limbic response to cocaine cues

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ABSTRACT

Drug-reward cues trigger motivational circuitry, a response linked to drug-seeking in animals and in humans. Adverse life events have been reported to increase sensitivity to drug rewards and to bolster drug reward signaling. Therefore, we hypothesized that cocaine-dependent individuals with prior emotional, physical and sexual abuse might have a heightened mesolimbic brain response to cues for drug reward in a new brief-cue probe. Cocaine-dependent human individuals (N = 68) were stabilized in an inpatient setting and then completed an event-related blood-oxygen-level dependent functional magnetic resonance imaging task featuring 500-ms evocative (cocaine, sexual, aversive) and comparator (neutral) cues. Responses to three questions about emotional, physical and sexual abuse from the Addiction Severity Index were used to divide the patients into subgroups (history of Abuse [n = 40] versus No Abuse [n = 28]). When subjects were grouped by the historical presence or absence of emotional, physical or sexual abuse, the Abuse group showed a heightened midbrain, thalamic, caudate, and caudal orbitofrontal cortex response to cocaine cues; a similar result was found in other evocative cues, as well. These findings are the first reported for a 500-ms cocaine-cue probe, and they highlight the ability of very brief evocative cues to activate the brain’s motivational circuitry. Although all participants had severe cocaine use disorders, individuals reporting prior abuse had a heightened mesolimbic response to evocative cues. To our knowledge, this is the first study in humans linking a history of abuse to a brain vulnerability (heightened mesolimbic response to drug cues) previously shown to contribute to drug-seeking.

Keywords Abuse, addiction, cocaine, fMRI, limbic, stress.

INTRODUCTION

Individuals with substance-use disorders face a multitude of problems, including issues related to health, social and family relations, occupation, criminal justice and homelessness (National Institute on Drug Abuse 2007). Among these issues is an overrepresentation of prior physical and sexual abuse, with rates up to 50 percent in some samples (Ouimette et al. 2000; Rice et al. 2001; Rosen et al. 2002; Pirard et al. 2005; Charney, Palacios-Boix, & Gill 2007). In one study, when emotional abuse was assessed, as well, 59 percent of people with addiction reported at least one type of abuse (Rice et al. 2001). The abuse rates in these studies were captured by questions from the Addiction Severity Index (ASI) (McLellan et al. 1992), which fortunately are similar in content and structure to other brief questionnaires commonly used to measure abuse (Gil-Rivas et al. 1997; Felitti et al. 1998).

Abuse can be experienced as an acute or chronic stressor (Hyman, Paliwal, & Sinha 2007; Sinha 2008). There is a well-established connection between psychological stress and addiction (Koob and Volkow, 2010). Importantly, just as there is an overlap in the prevalence of stress and addiction (E. Goeders 2003; Sinha 2008; See & Waters 2010; Bossert et al. 2013) there is also an overlap of stress and reward signaling in the brain (D’Angio et al. 1987; Sorg & Kalivas 1991; Rougé-Pont et al. 1993). We hypothesize that even within an addicted
population, the presence or lack of abuse in one’s history may create brain differences in response to external, motivationally significant stimuli.

Indeed, studies have shown that abuse is associated with modulated dopamine signaling in mesolimbic brain regions (Prueßner et al. 2004; Dillon et al. 2009), comprised of areas that process drug and non-drug rewards. Extensive research has linked stress and reward signaling to drug seeking in animals (Belin et al. 2013; Saal et al. 2003; Wise, 2004) and to relapse in humans (Fatseas et al., 2011; McHugh et al., 2004; Stewart, 2000).

Researchers have posited that a history of abuse might be associated with stress-related problems like relapse (Hyman et al., 2007), but how that might be reflected at the level of the brain has only recently begun to be addressed (Elton et al., 2015). Our own lab (Childress et al., 1999; Franklin et al. 2007; Langleben et al., 2008; Wetherill et al. 2014; Young et al. 2014) and others (Chase et al. 2011; Kühn & Gallinat 2011) have shown that drug cues activate motivational circuits. The brain findings are robust, but there is intriguing individual variability (Jasinska et al., 2014)—and it could reflect historical variables, such as abuse. Thus, we set out to investigate whether lifetime abuse would be reflected in the response of mesolimbic circuitry to cocaine cues. Given the interaction of stress and reward circuitry, we predicted that individuals with cocaine-use disorders and a history of abuse might have an enhanced response to cocaine cues, as compared to their non-abused counterparts.

Finally, previous work in the lab has often focused on the first half of the task to minimize the contribution of ‘carryover arousal’ as the task progresses. However, as highlighted by research on fear and anxiety (Plichta et al. 2014), the temporal dynamics of brain responding can reveal pathology (Swartz et al. 2013). For example, individuals with greater anxiety (Hare et al. 2008) tend to have a persistent brain response to repeated emotional stimuli. Similarily, individuals with autism have a more persistent response even to repeated neutral stimuli than controls (Swartz et al. 2013). Potentially relevant to the present study, individuals with posttraumatic stress disorder show a non-reducing brain response to repeated emotionally significant stimuli (Hendler, Rotstein, & Hadar 2001). Adopting this approach for the current study, we explicitly examined both the first and second half of the task in order to fully characterize the response profiles for the Abuse and NoAbuse phenotypes.

**METHODS**

**Participants**

Sixty-eight treatment-seeking, cocaine-dependent participants from successive cohorts at our center were included in the current analyses. They met standard eligibility for imaging studies, criteria described previously (Wetherill et al. 2014; Young et al. 2014). Briefly, they reported cocaine use on at least 8 of the last 30 days, and they were available for a 7–10 inpatient stay. Participants reported smoking as the primary route of cocaine administration. Exclusion criteria included: contraindications for functional magnetic resonance imaging (fMRI), use of medications that might affect dopamine transmission, a history of psychosis, seizures, or other organic brain syndrome, clinically significant cardiovascular, hematologic, hepatic, renal, neurological, or endocrine abnormalities, or a history of head trauma or injury. The Mini International Neuropsychiatric Interview was used to screen for psychiatric disorders (Sheehan et al. 1998). Other than cocaine dependence, participants with current Axis I psychiatric diagnoses were generally excluded, with the following exceptions: nicotine dependence, marijuana dependence and alcohol dependence not requiring detoxification. Individuals with current depression linked solely to periods of cocaine use/cessation were not excluded.

**Study design**

The basic features of our study design have been described previously (Childress et al. 2008). Briefly, participants were stabilized in a controlled, inpatient setting for 3–5 days to minimize the contribution of either cocaine intoxication or cessation symptoms. After stabilization, subjects participated in a scanning session that included a ‘fast’ event-related fMRI task (Fig. 1) with 24 novel 500-ms target cues in four categories (cocaine, sexual, aversive, neutral). Although, the current study is the first to examine a 500-ms duration, it is otherwise modeled closely after our prior event-related cocaine studies (Childress et al. 2008; Young et al. 2014). The cocaine cues (e.g. images of smoked cocaine, paraphernalia, etc.) and neutral cues (household or office objects; outdoor scenes) were from laboratory archives. The sexual and aversive cues were selected from the top quartile (e.g. ‘most pleasant’ and ‘most unpleasant’, respectively) of the International Affective Picture System (Lang et al. 1999). The targets were presented in a quasi-random order (no more than two of a kind in sequence), with an average 1500-ms interstimulus interval (gray screen with cross-hair). Twenty-four unique cues in each category were presented once and then repeated, for a total of 48 presentations per category. Thus, the task entailed two halves with 24 presentations of each cue category.

**Abuse versus NoAbuse subgroups**

Participants were subdivided into two groups based on three items from the ASI probing whether individuals

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experienced physical, sexual or emotional abuse at any point in their lifetime perpetrated by family members (e.g. mother, father, siblings partner/spouse, other family) or friends (e.g. close friends, neighbors, co-workers). Using the ASI allowed us to extract abuse information from more than ten years of data collection from cocaine patients. Previous studies have used ASI as a measure for abuse (Ouimette et al. 2000; Rosen et al. 2002; Pirard et al. 2005; Charney et al. 2007). The ASI has been found to have better selectivity than sensitivity compared to other measures (Najavits et al. 1998; Langeland, Draijer, & van den Brink 2003), and the ASI probes are similar to other studies examining abuse (Gil-Rivas et al. 1997; Felitti et al. 1998): ‘Did any of these people (family members, friends, etc) abuse you (1) physically (cause you physical harm)?; (2) sexually (force sexual advances or sexual acts)?; or (3) emotionally (make you feel bad through harsh words)?’. If participants reported abuse at any point in their lives, in any of the three categories (physical, sexual or emotional abuse), that participant was included in the ‘Abuse’ group. If an individual reported no abuse in all of the three categories, that participant was included in the ‘NoAbuse’ group.

fMRI acquisition

As described previously (Childress et al. 2008; Young et al. 2014), a Siemens 3 T scanner was used for acquisition of blood-oxygen-level dependent images. For normalization and coregistration purposes, a 5-min high-resolution 3-Dimensional T1-weighted (MPRAGE) structural scan was acquired with the following parameters: repetition time (TR) 1620 ms; echo time (TE) 3.87 ms; 160 slices; slice thickness 1 mm; matrix 192 × 256; flip angle 15°. Functional images were acquired via a T2*-weighted single-shot gradient-echo, planar-imaging sequence with the following parameters: TR 2000 ms; TE 30 ms; 33 interleaved slices; slice thickness 3 mm without any gap between adjacent slices; FOV 192 mm; matrix 64 × 64; flip angle 80°.

Data analysis

fMRI data were preprocessed using Statistical Parametric Mapping (SPM8; Wellcome Department of Cognitive Neurology, London, UK) batch mode scripts modified from ASLtbx. The processing steps were the same as in our previous study (Young et al. 2014), including slice timing correction, motion correction, temporal filtering, spatial smoothing and registration to the Montreal Neurological Institute (MNI) standard brain. The motion time courses were further removed from fMRI data using simple regression. Spatial smoothing was performed with an 8-mm³ full-width half-maximum Gaussian kernel.

Statistical analysis was performed with a general linear model using a canonical hemodynamic response function with both the first (time) and the second (dispersion) derivatives. Following the previously described design (see study design section above), we defined six first-level contrasts to assess the cue effects: cocaine versus neutral (first and second half), sex versus neutral (first and second half) and aversive versus neutral (first and second half).
Based on several studies reporting cue reactivity in limbic regions, we limit our main results to a priori regions of interest or ROIs (e.g. ventral tegmental area, amygdala, ventral striatum, midbrain, caudal orbitofrontal cortex [cOFC]), as well as other addiction-relevant regions, such as the insula (Naqvi & Bechara 2010), dorsal striatum (Everitt & Robbins 2013) and thalamus (Asensio et al. 2010). Regions of interest were identified using xjview (http://www.alivelearn.net/xjview8/) and FSL (Functional MRI of the Brain [FMRIB] Software Library, Oxford Centre for FMRIB). The ROI mask was created by first identifying anatomical regions (cOFC, striatum [caudate, putamen, ventral striatum], midbrain (VTA), anterior insula, amygdala and hippocampus) with fslview. Then, anatomical regions were thresholded, made into binary maps and added together into one mask with fslmaths.

We calculated a group by cue (2 × 3) ANOVA with GLM Flex Fast 2 (http://mrtools.mgh.harvard.edu) for each half of the task and examined the results of functional ROIs based on significant main effects of group for each half. Clusters from both of the ANOVA were considered significant at p < 0.01, corrected using Monte-Carlo (AFNI. 3dClustSim: http://afni.nimh.nih.gov). Parameter estimates (beta weights) for the functional clusters were extracted using Marsbar (http://marsbar.sourceforge.net); they were then imported into MATLAB (The Mathworks, Inc., Natick, Massachusetts, USA) for generating F values and for plotting.

For our primary analysis examining the Abuse versus NoAbuse groups on cue responding, independent t-tests were conducted for each cue type (for each half of the task). T-tests were considered significant at p < 0.01, corrected using Monte-Carlo (AFNI. 3dClustSim software: http://afni.nimh.nih.gov). Our results and discussions focus on regions overlapping our ROI mask (Fig. 1); however, we also present cluster-corrected whole brain results.

RESULTS

Demographics and clinical results

Participants were cocaine-dependent males averaging 44.4 years of age and 17.2 years of cocaine use. Most were African–American (89.9 percent) with an average of 12.5 years of education. Participants averaged 17.6 years of alcohol use; 42 percent used marijuana and 3 percent used heroin.

Prevalence of lifetime abuse

Forty individuals (59 percent) reported a history of any type of abuse (Table 1). Of these 40 individuals in the Abuse group, 36 reported emotional abuse, 20 reported physical abuse and 12 reported sexual abuse, and more than half reported two or more types of abuse (Table 1). The reports of abuse in the successive cohorts from our center were similar to previous reports (Ouimette et al. 2000; Pirard et al. 2005; Charney et al. 2007), including a sample with more than a thousand individuals with substance-use disorders (Rice et al. 2001). This suggests that our cohort was representative of a larger whole and underscores the ability of the ASI to capture the relevant phenotype (lifetime abuse).

Imaging results

Abuse versus No Abuse ANOVA results

The 2 × 3 ANOVA revealed a main effect of group (F(1,66) = 7.36, p = 0.009) in a thalamus cluster (that extended to midbrain and caudate) in the first half of the task. In the second half, there was a main effect of group (F(1,66) = 10.53, p = 0.002) in a cOFC cluster (that extended to the medial temporal lobe). Overall, the Abuse group had a greater response to the evocative cues, compared to the NoAbuse group (not shown). There was also a main effect of cues in a large interconnected thalamus/caudate cluster (F(2,66) = 9.75, p = 0.001) in the first half of the task (not shown) but no significant interactions survived cluster correction.

Abuse versus NoAbuse: drug cues

Overall, participants (N = 68) exhibited a robust and widespread mesolimbic response to drug cues. However, this pattern was more evident in the Abuse group (N = 40) than the NoAbuse group (N = 28, Fig. 2) and occurred in both halves of the task. Independent t-tests, corrected at the ROI mask level (p < 0.01, k > 147), revealed that the Abuse group had a greater response

<table>
<thead>
<tr>
<th>Table 1 Demographics and reported abuse.</th>
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<tbody>
<tr>
<td>Demographics</td>
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<tr>
<td>Gender</td>
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<tr>
<td>Race</td>
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<td>Age</td>
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<tr>
<td>Education</td>
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<tr>
<td>Cocaine use</td>
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<td>Alcohol use</td>
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<td>Cannabis use</td>
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<td>Heroin use</td>
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<tr>
<td>History of abuse</td>
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<tr>
<td>Any abuse</td>
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<tr>
<td>Emotional</td>
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<tr>
<td>Physical</td>
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<tr>
<td>Sexual</td>
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<td>Two or more</td>
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*p: Note: When p values could not be calculated, it is indicated by a ‘—’. 

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to drug cues in a thalamus/caudate/midbrain cluster (peak $t = 2.98$) during the first half of the task (Fig. 3). The Abuse group also had a greater response to drug cues in a cluster that included the cOFC (peak $t = 4.74$) in the second half of the task (Fig. 3). For purposes of demonstrating that the NoAbuse group had a differential response to drug (versus neutral) cues, we also present images from the NoAbuse group in the Supporting Information (Supplemental Fig. 1).

Clusters found with whole brain correction ($k > 265$) outside of the ROI mask for drug cues are reported in Table 2.

Abuse versus NoAbuse: comparator cues

For the comparator cues, the differences between Abuse and NoAbuse were limited to one half of the task or the other. In response to sexual cues differences between Abuse and NoAbuse groups were evident only in the second half of the task in a left cOFC (peak $t = 3.47$, Fig. 3b). Finally, for the aversive cues, differences between Abuse and NoAbuse were found only in the first half of the task in a thalamic/midbrain cluster (peak $t = 3.39$, Fig. 3c).

Clusters found with whole brain correction ($k > 265$) outside of the ROI mask for sexual and aversive cues are reported in Table 2.

Abuse versus NoAbuse: temporal pattern

To examine the general temporal patterns across the task, we collapsed across the three cue categories and plotted responding for the two significant clusters from the main effect of group (Abuse versus NoAbuse) in the whole-brain analysis. As shown in Fig. 4, the impact of the Abuse phenotype was expressed differently for the two clusters. For the cOFC cluster, responding was similar between the two groups in the first half but diverged in the second half of the task, with sustained responding in the Abuse group but decreased responding in the NoAbuse group (Fig. 4). For the thalamus/caudate cluster, the Abuse group showed a large initial response, but responding was low and similar for the two groups in the second half of the task (Fig. 4).

DISCUSSION

Mesolimbic brain response to 500-ms evocative cues differed between individuals with cocaine-use disorders, depending upon abuse history. As predicted, individuals with cocaine-use disorders and a history of abuse had a greater mesolimbic response to cocaine cues compared to those without lifetime abuse. These differential neurobiological results were evident in two main clusters, one that included the thalamus, midbrain and caudate and another that included the left caudal OFC and left parahippocampus. These results are novel in two ways. First, they are the first to show a response to brief 500-ms cues, a response that is similar to previous studies with different cue lengths (Childress et al. 1999, 2008; Volkow et al. 2006). Second, though a recent study found a link between abuse and cortical activation (Elton et al.,...
the present results are the first to show that lifetime abuse is associated with a heightened mesolimbic response to cocaine cues in a human population with substance-use disorders.

Prior studies have mostly looked at magnitude as a marker of vulnerability between patients and controls. The current study allowed us to look at temporal patterns of responding as related to abuse history. Our examination of the temporal patterns in the task showed that the Abuse phenotype could be expressed in more than one way, depending on brain region. In the thalamus/caudate cluster, the response pattern was initially large but reducing; this ‘early’ response in cue tasks may reflect clinically-relevant vulnerability. In the cOFC, the response pattern was sustained, consistent with reports of non-reducing responses to repeated stimuli in other pathologies (Hendler et al. 2001; Hare et al. 2008; Swartz et al. 2013; Plichta et al. 2014). Ongoing and prospective studies will allow for the examination of whether response magnitude, temporal dynamics or both have greater clinical relevance.

Previous research has reported the effect of prior abuse on brain activity to negative stimuli (Damnowski et al. 2012); however, that lifetime abuse was linked to...
Table 2  A priori mask and whole brain results: Abuse > NoAbuse at p < 0.01, cluster-corrected.

<table>
<thead>
<tr>
<th>Regions</th>
<th>Cluster Size</th>
<th>T value</th>
<th>P value</th>
<th>Coordinates</th>
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<tbody>
<tr>
<td>(A priori mask)</td>
<td>(k &gt; 147)</td>
<td>(uncorrected)</td>
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<tr>
<td>Drug1 – Neutral1</td>
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<tr>
<td>Thalamus/caudate</td>
<td>342</td>
<td>2.98</td>
<td>0.002</td>
<td>2</td>
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<tr>
<td>Aversive1 – Neutral1</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Nidbrain</td>
<td>235</td>
<td>3.39</td>
<td>0.001</td>
<td>4</td>
</tr>
<tr>
<td>Drug2 – Neutral2</td>
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</tr>
<tr>
<td>Caudal OFC/Amyg (Left)</td>
<td>487</td>
<td>4.74</td>
<td>&lt;0.001</td>
<td>-20</td>
</tr>
<tr>
<td>Sexual2 – Neutral2</td>
<td>168</td>
<td>3.47</td>
<td>&lt;0.001</td>
<td>-22</td>
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</table>

<table>
<thead>
<tr>
<th>(Outside the mask)</th>
<th>(k &gt; 265)</th>
<th>(uncorrected)</th>
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<tr>
<td>Drug1 – Neutral1</td>
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<tr>
<td>PCC/Precuneus</td>
<td>274</td>
<td>3.10</td>
<td>0.001</td>
<td>2</td>
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<tr>
<td>Sexual1 – Neutral1</td>
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<tr>
<td>Cerebellar (VVI, Left)</td>
<td>370</td>
<td>2.90</td>
<td>0.003</td>
<td>-22</td>
</tr>
<tr>
<td>Drug2 – Neutral2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sup. Occipital (Left)</td>
<td>756</td>
<td>3.69</td>
<td>&lt;0.001</td>
<td>-50</td>
</tr>
<tr>
<td>dIPFC (Right)</td>
<td>272</td>
<td>3.26</td>
<td>0.001</td>
<td>40</td>
</tr>
<tr>
<td>Sexual2 – Neutral2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dIPFC (Right)</td>
<td>409</td>
<td>3.26</td>
<td>0.001</td>
<td>44</td>
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</table>

differential response to appetitive cues may seem counter-intuitive. The impact of adverse events on reward signaling has several dimensions. Pre-clinical and clinical studies have found that stress increases drug-seeking and drug-taking behaviors (Sinha 2001) and produces an increase in dopamine signaling (Louilot, Le Moal, & Simon 1986; Sorg & Kalivas 1991; Rougé-Pont et al. 1993; Pruessner et al. 2004). Studies of significant stress, like prior abuse, have revealed reduced mesolimbic brain-region volume (Weniger et al. 2008; Dannlowski et al. 2012; Van Dam et al. 2014) as well as blunted mesolimbic response to cues linked with monetary rewards (Dillon et al. 2009; Elman et al. 2009; Mehta et al. 2009; Goff et al. 2013). In contrast, prior abuse was associated with increased mesolimbic response to a stimulant (amphetamine) and emotional stimuli in non-addicted males (Dannlowski et al. 2012; Oswald et al. 2014). At this stage of the literature, there are several differences across studies that may account for differences in results: (1) the nature of the populations (e.g. adult cocaine users versus adolescents or non-addicted adults); (2) cues (e.g. evocative versus reward anticipation); (3) a potentially non-linear relationship of severity of stress and brain response (e.g. linear versus inverted U); and (4) anatomical regions (e.g. heightened VTA and amygdala versus blunted ventral striatum). With these several differences, future studies will be needed to disentangle the nature and direction of the effects of prior trauma on brain responding to various probes.

To our knowledge, this is the first study showing that addicted individuals with prior abuse have a greater limbic response to cues signaling their preferred drug. Further, this enhanced reactivity extended to both the appetitive and aversive domains. This might occur because, from an evolutionary perspective, the promise of reward or the threat of danger may take on increased salience for an individual who has survived danger but whose future may be uncertain or short-lived. From another perspective, the heightened mesolimbic response to cues in a subset of our clinical population also has parallels to findings in the pre-clinical literature on incentive salience (Robinson & Berridge 1993). A subgroup of individuals (‘sign-trackers’) in the general population are more responsive to signals for reward (Flagel et al. 2010) even without prior stress; these results have recently been extended to the aversive domain (Morrow, Maren, & Robinson 2011; Morrow et al. 2015). These two viewpoints (evolutionary and incentive salience) may actually be complementary, in that a subgroup of individuals could be inherently more cue-reactive, but a history of stress or abuse may enhance or even create this vulnerability (Lomanowska et al. 2011).
As with any initial finding, there are limitations that can guide further research. For ethical reasons, human studies of abuse necessarily rely upon self-report; future pre-clinical studies can determine how various stressor parameters (e.g. type, frequency and developmental stage) impact the learned response to drug cues. A basic issue with new findings is generalizability: the present study investigated older males with a chronic cocaine-use history. Future studies can determine generalizability of the current abuse findings to different clinical populations (differing in age, gender, type of addiction), to other brain-behavioral probes (e.g. for inhibition). The study was limited to self-report of lifetime abuse using the ASI as a measure. The ASI captured both childhood and adult abuse, but did not specify when specific abuses occurred. Even without temporal sensitivity, this simple tool clearly separated clinical phenotypes (e.g. Abuse versus NoAbuse) with measurable brain differences. As the study was retrospective, we were limited to available tools already collected (e.g. no measures related directly to stress, such as cortisol), but future research will utilize multiple item abuse probes (e.g. Child Trauma Questionnaire [CTQ]), which will allow for a comparison of abuse reported from the ASI versus the CTQ and to obtain information about abuse occurring before the age of 15. Finally, our imaging cohort did not include participants with any DSM IV Axis 1 comorbid mood or anxiety disorders. Thus, future studies may include or even explicitly study the impact of these diagnoses (Hart & Rubia 2012), especially because psychopathology is often more severe in populations with lifetime abuse (Rice et al. 2001; Pirard et al. 2005; Charney et al. 2007). Worth noting, inclusion of individuals with common comorbidities (e.g. depression, anxiety, post-traumatic stress disorder) would not necessarily be expected to undermine our results, and could even enhance them.

Physical, sexual and emotional abuse affects millions of people every year and is highly correlated with addiction (Felitti et al. 1998). As discussed, abuse can have dramatic effects on the brain (for a review, see [Hart & Rubia 2012]). Research on the effects of abuse on addiction trajectory and outcome has been mixed (Gil-Rivas et al. 1997; Pirard et al. 2005; Charney et al. 2007), but a recent study suggests that abuse predicts relapse (Van Dam et al. 2014). Thus, identifying brain systems affected by abuse may not only help us understand the harsh impacts of the past, but could also guide targeted interventions to help ’reset’ these systems thus improving the odds of recovery for our future patients.

**AUTHOR CONTRIBUTIONS**

PR, AT and ARC contributed to study concept. PR performed all second-level analyses. KJ performed all first-level analyses. ARC, ZM, KJ and ZW assisted with data analysis. ARC and PR were responsible for interpretation of findings. ARC, TF and DL were responsible for study design. JS, MG, KK and ZM assisted with data collection. PR and ARC drafted the manuscript. TR and RW provided critical assessment of manuscript revision; COB and KY edited the manuscript for accuracy. All authors critically reviewed content and approved final version for publication.

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References


**SUPPORTING INFORMATION**

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site:

**Supplemental Figure 1.** Individuals without a history of abuse and their response to Drug minus Neutral (threshold 2 < t < 5, first half). At this reduced threshold (compared to Figure 2), the NoAbuse group had activity within some of the ROI mask regions, such as the striatum and anterior insula.