Published in final edited form as:

Drug Alcohol Depend. 2016 January 1; 158: 76–85. doi:10.1016/j.drugalcdep.2015.11.012.

Prenatal cocaine exposure, illicit-substance use and stress and craving processes during adolescence

Sarah W. Yip^{a,*}, Cheryl M. Lacadie^b, Rajita Sinha^{c,d,e}, Linda C. Mayes^{d,f}, and Marc N. Potenza^{a,c,d,e}

^aCASAColumbia, Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut

^bDepartment of Diagnostic Radiology, Yale University School of Medicine, New Haven, Connecticut

^cDepartment of Psychiatry, Yale University School of Medicine, New Haven, Connecticut

^dChild Study Center, Yale University School of Medicine, New Haven, Connecticut

^eDepartment of Neurobiology, Yale University School of Medicine, New Haven, Connecticut

^fDepartments of Epidemiology, Pediatrics and Psychology, Yale University School of Medicine, New Haven, Connecticut

Abstract

Background—Prenatal cocaine exposure (PCE) is associated with increased rates of illicit-substance use during adolescence. In addition, both PCE and illicit-substance use are associated with alterations in cortico-striato-limbic neurocircuitry, development of which is ongoing throughout adolescence. However, the relationship between illicit-substance use, PCE and functional neural responses has not previously been assessed concurrently.

*Address for correspondence: Sarah W. Yip, 1 Church Street, 7th Floor, Suite 701, New Haven, CT, 06511; Phone: 203-704-7588; Fax: 203-737-3591; sarah.yip@yale.edu.

Supplementary material can be found by accessing the online version of this paper at <http://dx.doi.org> and by entering doi:...

Contributors: LCM, RS and MP designed the study protocols. CML conducted fMRI data analyses in consultation with SWY and MP. SWY wrote the first draft of the manuscript and worked with all other authors on subsequent drafts. All authors have approved this manuscript.

Conflict of interest: The authors report no financial conflicts of interest with respect to the content of this manuscript. Dr. Potenza has received financial support or compensation for the following: Dr. Potenza has consulted for and advised Boehringer Ingelheim, Lundbeck, Ironwood, Shire and INSYS; has consulted for and has financial interests in Somaxon; has received research support from the National Institutes of Health, Veteran's Administration, Mohegan Sun Casino, the National Center for Responsible Gaming and its affiliated Institute for Research on Gambling Disorders, and Forest Laboratories, Ortho-McNeil, Oy-Control/Biotie, Glaxo-SmithKline, and Psyadon pharmaceuticals; has participated in surveys, mailings or telephone consultations related to drug addiction, impulse control disorders or other health topics; has consulted for gambling entities, law offices and the federal public defender's office in issues related to impulse control disorders; provides clinical care in the Connecticut Department of Mental Health and Addiction Services Problem Gambling Services Program; has performed grant reviews for the National Institutes of Health and other agencies; has guest-edited journal sections; has given academic lectures in grand rounds, CME events and other clinical or scientific venues; and has generated books or book chapters for publishers of mental health texts.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Methods—Sixty-eight adolescents were recruited from an ongoing longitudinal study of childhood and adolescent development. All participants had been followed since birth. Functional magnetic resonance imaging (fMRI) data were acquired during presentation of personalized stressful, favorite-food and neutral/relaxing imagery scripts and compared between 46 PCE and 22 non-prenatally-drug-exposed (NDE) adolescents with and without lifetime illicit-substance use initiation. Data were analyzed using multi-level ANOVAs ($p_{FWE} < .05$).

Results—There was a significant three-way interaction between illicit-substance use, PCE status and cue condition on neural responses within primarily cortical brain regions, including regions of the left and right insula. Among PCE versus NDE adolescents, illicit-substance use was associated with decreased subcortical and increased cortical activity during the favorite-food condition, whereas the opposite pattern of activation was observed during the neutral/relaxing condition. Among PCE versus NDE adolescents, illicit-substance use during stress processing was associated with decreased activity in cortical and subcortical regions including amygdala, hippocampus and prefrontal cortex. Neural activity within cortico-striato-limbic regions was significantly negatively associated with subjective ratings of anxiety and craving among illicit-substance users, but not among non-users.

Conclusions—These findings suggest different neural substrates of experimentation with illicit drugs between adolescents with and without *in utero* cocaine exposure.

Keywords

development; addiction; emotion; cocaine; cannabis; fMRI

1. INTRODUCTION

Development of cortico-striato-limbic neurocircuitry is ongoing throughout adolescence (Gogtay and Thompson, 2010; Wahlstrom et al., 2010). These circuits subserve processes including emotion regulation, reward processing and motivational control and are critically involved in addiction vulnerability (Chambers et al., 2003; Andersen and Teicher, 2008). Preclinical data have demonstrated significant effects of prenatal cocaine exposure (PCE) on these systems (Glatt et al., 2000; Harvey et al., 2001; Stanwood et al., 2001a, 2001b; Harvey, 2004; Malanga et al., 2008; McCarthy and Bhide, 2012; Wang et al., 2013), which may relate to the elevated rates of illicit-substance use reported among human adolescents with PCE (Delaney-Black et al., 2011; Richardson et al., 2013). In humans, functional magnetic resonance imaging (fMRI) data indicate alterations in cortico-striato-limbic neurocircuitry among adolescents with PCE (Yip et al., 2014). However, the relationship between these alterations and illicit-substance-use behaviors during adolescence has not been assessed previously. Such research may identify neurodevelopmental factors influencing illicit-substance-use initiation in this vulnerable population.

In this study, we assessed the interactive and main effects of lifetime illicit-substance use, PCE status and cue condition (stressful, appetitive or neutral-relaxing) on neural activations among 68 adolescents recruited from an ongoing longitudinal study of child and adolescent development (Mayes et al., 2005). Given the high rates of individual variability associated with the processing of affective stimuli (Hamann, 2004; Sinha, 2009), we utilized a well-

validated, guided-imagery fMRI task that allows for both personalization of stimuli on an individual basis, as well as standardization of emotional valence across individuals (Sinha, 2009).

Our previous research indicated reduced ventral striatal, anterior cingulate and prefrontal cortical (PFC) activations among PCE adolescents during exposure to favorite-food cues, but not during exposure to stressful cues, suggesting possible interaction effects between cue condition (appetitive, stressful or neutral-relaxing) and PCE status (Yip et al., 2014). Studies conducted in adult substance-dependent populations have further demonstrated significant effects of cocaine-use within insular-striatal regions (Potenza et al., 2012; McHugh et al., 2013; Patel et al., 2013), and data suggest alterations within these circuits among young adults at increased risk for addictions (Stewart et al., 2013; Harle et al., 2014; Yip et al., 2015). Based on these findings, we hypothesized that there would be a three-way interaction between illicit-substance use initiation, PCE status and cue condition on cortico-striato-limbic activations. We further anticipated that this interaction would involve decreased subcortical limbic activity during exposure to stressful and appetitive (favorite-food) cues amongst PCE (versus non-prenatally drug-exposed; NDE) adolescents with illicit-substance use. Finally, we hypothesized that subjective measures of anxiety and food craving would relate differently to neural activations based on illicit-substance-use status, as has been reported in previous studies of adults (Sinha et al., 2005).

2. METHODS

2.1. Participants and recruitment

2.1.1. Recruitment of mothers with and without drug use during pregnancy—

All participants in this study were recruited from an ongoing study of adolescents who have been followed longitudinally since birth (Mayes et al., 2005). For this study, mothers were recruited over a 5-year period from a large urban hospital setting (Rando et al., 2013). Maternal cocaine-use was determined based on maternal self-report and on urine toxicology during pregnancy or following delivery. Cocaine-using mothers also reported perinatal tobacco use (n=14; 30.4%), perinatal alcohol use (n=11, 23.9%) and perinatal cannabis use (n=19; 41.3%).

2.1.2. Adolescents with and without prenatal cocaine exposure—

At the time of this study youth in the larger cohort who had been followed since birth and took part in bi-annual assessments were between the ages of 11 and 17 (n=371) (Chaplin et al., 2010).

Based on information from these assessments, adolescents aged 14 to 17 who had no serious psychiatric or medical condition were invited to participate in the fMRI study, resulting in a total of eighty-seven adolescents (59 PCE) from the longitudinal cohort who participated in fMRI during the personalized guided-imagery task. At the time of MRI scanning, the mean ages of PCE and NDE adolescents was 14.9 years and 14.5 years, respectively. This information is shown in Table 1, along with other demographic and clinical variables.

Adolescents were assessed using the National Institute of Health Diagnostic Interview Schedule for Children (C-DISC-4.0-Y) (Shaffer et al., 2000) and none met criteria for any

Axis-I disorder (including substance use disorders). After complete description of the study to the subjects, written informed consent was obtained.

We have previously published findings from between-group comparisons of fMRI data from a subset of the PCE (n=22) and NDE (n=22) adolescents included in this manuscript (Yip et al., 2014). A separate publication exploring the effects of childhood trauma on neural responses among adolescents from the longitudinal cohort has also been published (Elsei et al., 2015). However, neither of these manuscripts assessed effects of substance use initiation on neural responses (aim of present study).

After excluding participants with insufficient or noisy data (e.g., due to excess motion, subjects falling asleep or becoming claustrophobic or technical difficulties with stimulus presentation; further details provided in Supplemental Materials), the final sample included 68 adolescents (46 PCE and 22 NDE adolescents). Rates of exclusion did not differ between PCE and NDE groups ($\chi^2_{(1)}=.25$, $p=.62$).

2.2. Illicit-substance-use initiation

Substance-use data were obtained via analysis of urine toxicology samples and self-report on the Youth Risk Behavior Survey. Illicit-substance use was defined as any positive self-report or urinalysis indicating cannabis, cocaine, opiate, crystal methamphetamine, lysergic acid diethylamide (LSD), phencyclidine (PCP), ecstasy (3,4-methylenedioxy-N-methylamphetamine; MDMA) or inhalant use at any visit during the ongoing longitudinal study and was coded as a dichotomous variable (yes/no). Adolescents meeting criteria for illicit-substance use at any time during the study period (2007 to 2011) were classified as 'illicit-substance users' for all subsequent analyses, whereas those individuals who did not meet criteria for illicit-substance use at any time point were classified as 'illicit-substance non-users'. Other substance-use data (tobacco and alcohol use) were also defined via urinalysis (cotinine or ethyl glucuronide, respectively) or self-report and details of these rates are given in Supplemental Tables 1 and 2¹.

2.3. Imagery script development and scanning procedures

During fMRI scanning, adolescents were presented with six personalized 2.5-minute audiotaped scripts (two neutral-relaxing, two stressful and two favorite-food), which were presented in a randomized, counter-balanced order. Stressful and favorite-food scripts were individually calibrated to ensure equivalent emotional valence across participants (see Supplemental Materials for further details on script generation). Heart rate was measured throughout the scan using a pulse oximeter. Participants provided ratings of subjective anxiety and food craving using a Likert-type scale ranging from 0 ('not at all') to 10 ('more than ever') immediately before and after each script presentation. Each script was preceded by a 1.5-minute baseline period and followed by a 1-minute quiet recovery period and a progressive relaxation period (approximately 2 minutes). In order to ensure that there were no residual effects of the previous script on each subsequent script, new trials were initiated

¹Supplementary material can be found by accessing the online version of this paper at <http://dx.doi.org> and by entering doi:...

only once the participants' heart rate and subjective ratings had returned to their previous pre-trial baseline rates. For further details on trial presentation, see Supplemental Figure 1².

2.4. Image acquisition and analysis

All images were acquired using a 3T Trio MRI using standard acquisition parameters (details in Supplemental Materials³). Functional imaging analyses were conducted using SPM5 (preprocessing; Wellcome Functional Imaging Laboratory, London, United Kingdom) and the BioImage Suite (www.bioimagesuite.org), as reported previously (e.g., Hommer et al., 2012; Yip et al., 2014). See Supplemental Materials for details on pre-processing and first-level analyses⁴.

Group-level random-effects models were conducted using AFNI Matlab library software (afni.nimh.nih.gov/afni/matlab) and proceeded in several steps. First, a three-way ANOVA including the between-subjects factors of illicit-substance use initiation (yes, no) and prenatal exposure status (PCE, NDE) and the within-subjects factor of task condition (stress, favorite-food, and neutral-relaxing) was conducted in order to test for interaction and main effects of these variables on neural activations. To explore further the nature of identified two-way and three-way-interaction findings, two-tailed t-tests were conducted to identify between-group differences (illicit-substance-users versus non-users) in BOLD signal responses during each of the three conditions separately (neutral-relaxing, stress, favorite-food) among PCE and NDE adolescents. Whole-brain correlational analyses were conducted in order to examine the relationships between brain activations and subjective ratings of anxiety and craving in adolescents with and without illicit-substance use. Family-wise-error (FWE) correction for multiple comparisons was conducted using a Monte-Carlo simulation with AlphaSim in AFNI (smoothing kernel = 6mm; cluster connectivity radius=6.296; 3.44mm × 3.44mm × 4mm; iterations of 1500). It was determined that at a value of $p < 0.05$ a cluster of 132 original voxels (6248mm³) would be necessary for FWE correction.

3. RESULTS

3.1. Demographic, clinical and substance use characteristics

Demographic characteristics of NDE and PCE adolescents are shown in Table 1. NDE and PCE adolescents did not differ in gender ($\chi^2_{(1)}=.15$, $p=.70$), race ($\chi^2_{(3)}=5.29$, $p=.15$), ethnicity (Hispanic/Non-Hispanic; $\chi^2_{(1)}=2.55$, $p=.11$), age ($F_{(1,66)}=3.04$, $p=.09$) or body mass index (BMI; $F_{(1,66)}=3.62$, $p=.06$). In comparison to NDE adolescents, PCE adolescents had lower estimated IQ scores ($F_{(1,59)}=4.47$, $p=0.04$), as assessed using the Kaufman Assessment Battery for Children (Kaufman AS and NL, 1983). In comparison to NDE adolescents, PCE adolescents had higher scores on the Childhood Trauma Questionnaire Short-Form (CTQ-SF; $F_{(1,62)}=4.42$, $p=0.04$).

At the time of scanning, three NDE adolescents and 21 PCE adolescents reported illicit-substance use initiation. During follow-up, an additional 7 NDE adolescents and 18 PCE

²Supplementary material can be found by accessing the online version of this paper at <http://dx.doi.org> and by entering doi:...

³Supplementary material can be found by accessing the online version of this paper at <http://dx.doi.org> and by entering doi:...

⁴Supplementary material can be found by accessing the online version of this paper at <http://dx.doi.org> and by entering doi:...

adolescents reported illicit-substance-use initiation. The final sample therefore included 49 (39 PCE) adolescents with lifetime illicit-substance use and 19 (7 PCE) adolescents without lifetime illicit-substance use. PCE and NDE illicit-substance users did not differ with respect to the timing of illicit-substance-use initiation (i.e., initiation pre- versus post-scan) ($\chi^2_{(1)}=1.81$, $p=.18$).

Consistent with previous findings (Delaney-Black et al., 2011; Richardson et al., 2013), significantly more PCE (versus NDE) adolescents met criteria for lifetime illicit-substance use ($\chi^2_{(1)}=11.43$, $p=.001$) and past-month use at the time of scanning ($\chi^2_{(1)}=6.51$, $p=.01$), although overall rates of use across the entire sample were relatively low (e.g., no participants met criteria for abuse or dependence).

Illicit-substance users versus illicit-substance non-users did not differ in age ($F_{(1,66)}=.67$, $p=.42$), race ($\chi^2_{(3)}=4.26$, $p=.24$), ethnicity ($\chi^2_{(1)}=.15$, $p=.67$), or BMI ($F_{(1,66)}=.32$, $p=.58$), but did differ in gender (illicit-substance users= 69.4% male; illicit-substance non-users=36.8% male; $\chi^2_{(1)}=6.06$, $p=.01$).

3.2. Subjective and physiological responses

Across all participants, anxiety ratings increased from baseline following exposure to stressful cues ($t_{(67)}=4.14$, $p=.0001$) and food craving ratings increased following exposure to favorite-food cues ($t_{(67)}=6.15$, $p<.0001$). Neither anxiety nor food-craving ratings increased from baseline following exposure to neutral-relaxing cues (p 's>.29). No significant differences in anxiety or craving ratings following cue exposure (post-exposure rating minus baseline) for any of the three cue conditions were observed between PCE versus NDE adolescents, or between illicit-substance users versus illicit-substance non-users (p 's>.08). Among PCE adolescents, illicit-substance users (versus illicit-substance non-users) had significantly lower anxiety ratings following exposure to neutral/relaxing cues ($F_{(45)}=6.45$, $p=.02$).

Due to technical problems with the pulse oximeter, heart-rate data were not available for three PCE participants. Across all participants, heart rate significantly increased from baseline following exposure to favorite-food cues ($t_{(64)}=2.78$, $p=.007$) but did not differ from baseline during exposure to neutral-relaxing or stressful cues (p 's>.43). There were no significant differences in heart rate during cue exposure (minus baseline) between PCE and NDE adolescents for any of the three cue conditions (p 's>.5). No significant differences in heart rate were found between illicit-substance users and illicit-substance non-users amongst PCE or NDE adolescents (p 's>.13).

3.3. Mixed-effects ANOVA

3.3.1. Main effects of illicit-substance use and cue-condition on neural responses—As shown in Table 2, there was a significant main effect of lifetime illicit-substance use on brain activations within regions including the thalamus, insula, hippocampus, caudate, anterior and posterior cingulate cortices and inferior frontal gyrus (IFG) and dorsolateral (DL) prefrontal cortex (PFC). There was a significant main effect of cue condition on brain activations within regions including the caudate, anterior cingulate,

thalamus, insula, brainstem and temporal pole. These results did not significantly change after co-varying for IQ and CTQ scores (Supplemental Figure 2⁵).

3.3.2. Three- and two-way interactions—Findings related to three- and two-way interactions from the mixed-effects ANOVA assessing illicit-substance use, PCE status and cue condition as related to neural activations are shown in Figure 1 and Table 3. A three-way interaction between PCE/NDE status, illicit-substance-use initiation and cue condition on brain activations was observed within brain regions including bilateral insula, inferior parietal lobule and superior temporal gyrus. As shown in Figure 1, this interaction involved greater insular activity among PCE adolescents with illicit-substance-use (versus those without) during the neutral-relaxing condition but not during the stressful or appetitive cue conditions (Figure 2).

There was a significant two-way interaction between PCE/NDE status and cue condition on brain activations within regions including the cuneus, posterior cingulate and primary and secondary visual cortices. A further two-way interaction was observed between substance-use-initiation status and PCE/NDE status on activations within regions including the middle occipital gyrus and associative visual cortex. There was no two-way interaction between illicit-substance use initiation and cue condition.

3.4. Between-group differences by cue condition

In order to further understand the nature of the three-way interaction effects, comparisons of neural activations among PCE versus NDE adolescents in relation to illicit-substance use were conducted using a ‘double-contrast’ of PCE adolescents (illicit-substance users – illicit-substance non-users) versus NDE adolescents (illicit-substance users – illicit-substance non-users) for each of the three cue conditions (Figure 2; further details in Supplemental Materials and in Supplemental Tables 3–5⁶).

3.4.1. Favorite-Food Cues—Among PCE versus NDE adolescents, illicit-substance use was associated with decreased activity within regions including the parahippocampal gyrus and cerebellum, accompanied by increased activity within the OFC and IFG during the favorite food condition.

3.4.2. Stress Cues—Among PCE versus NDE adolescents, illicit-substance use was associated with decreased activity within regions including the OFC, anterior PFC, anterior and posterior cingulate cortices, amygdala, hippocampus and brainstem during the stress condition.

3.4.3. Neutral-Relaxing Cues—Among PCE versus NDE adolescents, illicit-substance use was associated with increased activity within subcortical regions including the thalamus, brainstem, insula and putamen and decreased activity within regions including the anterior PFC and DLPFC during the neutral-relaxing condition.

⁵Supplementary material can be found by accessing the online version of this paper at <http://dx.doi.org> and by entering doi:...

⁶Supplementary material can be found by accessing the online version of this paper at <http://dx.doi.org> and by entering doi:...

3.5. Associations between subjective ratings of anxiety and craving and brain activations

Correlational analyses revealed significant associations between brain activations and subjective ratings of craving or anxiety among illicit-substance users (PCE and NDE combined), but not among illicit-substance non-users (Figure 3; Supplemental Table 7)⁷. Among illicit-substance users, anxiety negatively correlated with activity during the stress condition across multiple regions including the DLPFC, temporal poles, thalamus, putamen and anterior and posterior cingulate cortices. Among illicit-substance users, subjective food craving negatively correlated with activity during the favorite-food condition within regions including the caudate, anterior cingulate and DLPFC. Food craving also negatively correlated with activity during the neutral-relaxing condition within regions encompassing the PFC, caudate, putamen, thalamus, anterior and posterior cortices and temporal poles.

4. DISCUSSION

4.1. Overview

This study assessed the relationship between illicit-substance use initiation, PCE status and neural responses to appetitive, stressful and neutral-relaxing cues in a well-characterized sample of adolescents who have been followed longitudinally since birth (Mayes et al., 2005). Study findings suggest different neural substrates of experimentation with illicit-substances between adolescents with and without PCE.

4.2. Subjective and physiological measures

Across all participants, stressful and appetitive (but not neutral-relaxing) scripts were associated with increases in anxiety and craving ratings, respectively, indicating that the guided-imagery task was successful in eliciting the targeted emotional responses, as in previous studies (Potenza et al., 2012; Jastreboff et al., 2013). Subjective ratings did not differ as a function of PCE or illicit-substance use status following stressful or appetitive scripts. However, among PCE adolescents, illicit-substance users had significantly lower anxiety ratings than illicit-substance non-users following neutral-relaxing cues, suggesting that imagery-based relaxation techniques may be effective in reducing anxiety symptoms in this population (although this possibility remains to be examined systematically). No differences in heart rate during any of the three cue conditions were observed as a function of PCE or illicit-substance use status. These data indicate that our groups were relatively well matched on subjective and physiological measures; thus, these factors are unlikely to account for observed between-group differences in BOLD responses (discussed below).

4.3. Three-way interaction effects of prenatal cocaine exposure, illicit-substance use and cue-condition on neural responses

Partially consistent with our primary hypothesis, there was a significant three-way interaction between illicit-substance use status, PCE status and cue condition on neural responses during the guided-imagery task within cortical regions (e.g., bilateral insula, inferior parietal lobule, superior temporal gyrus) implicated in emotion regulation (Goldin et al., 2008) and craving processes (Kilts, 2004; Naqvi et al., 2014). This interaction involved

⁷Supplementary material can be found by accessing the online version of this paper at <http://dx.doi.org> and by entering doi:...

greater insular activity among PCE adolescents with illicit-substance use (versus those without) during the neutral-relaxing condition but not during the stressful or appetitive cue conditions. The insula is centrally involved in both affective and reward-related processing and is hypothesized to contribute to approach behaviors (e.g., substance-use initiation) via its role in interoceptive processing (Chung and Clark, 2014; Paulus and Stewart, 2014). Our finding of heightened insula reactivity among adolescents with PCE who experiment with drugs-of-abuse raise the possibility that neurodevelopmental factors might contribute to the insular cortex alterations observed in adults with cocaine dependence (Potenza et al., 2012; Cisler et al., 2013; McHugh et al., 2013; Patel et al., 2013), although this possibility warrants direct examination.

Partially contrary to our primary hypothesis, the three-way interaction effects did not extend into subcortical limbic regions, although findings from main effects analyses (of cue-condition) indicated that the guided-imagery task successfully recruited both cortical and subcortical regions (e.g., insula, anterior cingulate, caudate, thalamus, brainstem).

4.4. Between-group differences by cue condition

4.4.1. Favorite-Food Cues—Consistent with our second hypothesis, illicit-substance use among PCE versus NDE adolescents was associated with decreased subcortical activity in response to appetitive cues. This involved relatively decreased activity within regions including the parahippocampal gyrus and cerebellum and increased activity within prefrontal regions implicated in craving and motivational control processes (e.g., OFC, IFG; London, 2000; Goldstein and Volkow, 2011). Cognitive-control mechanisms subserved by these regions naturally mature across childhood and adolescence in typical development (Crone et al., 2004). These data suggest that development of these regions may be differentially altered among PCE versus NDE adolescents who are at-risk for, or have already begun, illicit-substance use. The direct clinical implications of these findings require further examination; however, it is possible that interventions specifically targeting cognitive-control processes may help to reduce rates of illicit-substance use among youth with PCE.

4.4.2. Stress Cues—Also consistent with our second hypothesis, illicit-substance use among PCE versus NDE adolescents was associated with decreased subcortical activity in response to stressful cues. This involved a pattern of relatively widespread reductions within subcortical regions (amygdala, hippocampus, brainstem) involved in stress responses and memory formation (Wolf, 2009), and was accompanied by similar reductions in cortical regions (anterior and posterior cingulate, anterior PFC, OFC) involved in higher-order processes related to the development of addictions; e.g., attention, decision-making, cognitive and motivational control processes (Goldstein and Volkow, 2011; Devito et al., 2013). These data suggest decreased neural processing of stress-related stimuli among PCE adolescents who experiment with illicit-substances, raising the possibility that relatively blunted stress responses may be a vulnerability factor for illicit-substance use in this population. Further longitudinal research specifically focusing on stress responses in this high-risk population is therefore warranted.

4.4.3. Neutral/Relaxing Cues—During the neutral/relaxing condition, illicit-substance use among PCE (versus NDE) adolescents was associated with increased activity within reward-related neurocircuitry (e.g., thalamus, striatum) and decreased activity within prefrontal-cortical regions involved in inhibitory and cognitive control processes (MacDonald, 2000; Goldstein and Volkow, 2011). This pattern of activation differs from that of generally decreased subcortical activity and increased cortical activity observed during the favorite-food condition. Together, these data suggest a general hyperactivation of ‘bottom-up’ reward circuits in the absence of compensatory ‘top-down’ activations and without the presence of an external, overtly rewarding stimulus among PCE adolescents who experiment with illicit-substances. More generally, these data suggest a differential relationship between corticolimbic neural function and illicit-substance use initiation among adolescents with and without *in utero* cocaine exposure.

4.5. Associations between neural responses and subjective ratings of anxiety and craving

Among adolescents with lifetime illicit-substance use initiation, significant negative associations between subjective ratings of anxiety and food craving were observed across all three conditions within cortical and limbic regions previously implicated in studies of adult cocaine dependence (Garavan, 2000; Kilts, 2001; Potenza et al., 2012). Specifically, neural responses during the stress condition were negatively correlated with anxiety ratings within prefrontal cortical and limbic regions, whereas neural responses during the favorite-food condition were negatively correlated with food craving ratings in similar, though not identical, brain regions. Although no increase in craving ratings was observed during exposure to neutral-relaxing cues, similar correlations between food craving ratings and neural responses were also observed during the neutral-relaxing condition among adolescents with lifetime illicit-substance use initiation. While preliminary, these findings suggest that limbic (e.g., caudate, putamen, thalamus) activity may be related to subjective experiences of low-level craving among adolescents who experiment with drugs-of-abuse, even in the absence of an overt appetitive stimulus.

No associations between subjective ratings of anxiety or craving and brain activations were seen among illicit-substance non-users for any of the three cue conditions. These findings suggest that neural responses within regions involved in emotional, motivational and reward processing (e.g., thalamus, striatum; Diener et al., 2012) may be more closely linked to subjective experiences of craving and anxiety amongst adolescents who experiment with illicit-substances versus those who do not. As such, it is possible that interventions providing skills training for dealing with negative emotional states such as anxiety and craving may be particularly effective in reducing adolescent substance use. However, further research is needed to test this hypothesis, as well as to establish the effect of skills training and other intervention strategies on limbic circuitry during adolescence.

4.6. Strengths and limitations

This study has several strengths, including the concurrent assessment of the main and interactive effects of multiple systems (*in utero* exposure, illicit-substance use, functional neural responses across different cue conditions), consistent with the growing recognition of the importance of studying dynamic neurodevelopmental trajectories (Casey et al., 2014).

This study also has several limitations which should be noted. Our groups were not well-matched for IQ or for trauma histories. Inclusion of these variables as covariates-of-no-interest in the whole-brain ANOVA did not significantly alter our findings. However, we cannot rule out the possibility of residual effects of these variables on between-group differences in neural responses. Consistent with the general literature, substance-use was more prevalent among PCE adolescents (Delaney-Black et al., 2011; Richardson et al., 2013), with approximately 85% of PCE adolescents versus 46% of NDE adolescents reporting lifetime illicit-substance use initiation. Our sample therefore included a relatively small numbers of PCE adolescent *without* illicit-use (n=7) and of NDE adolescents *with* illicit-use (n=10), which likely limited overall statistical power. These relatively small numbers are a consequence of the uniqueness of the study population - PCE and NDE youth of comparable age and BMI from the same inner-city sample who have been followed longitudinally since birth (Rando et al., 2013). Similarly, we were not sufficiently powered to explore within-group effects related to different types of illicit-substance use (e.g., mono- versus poly-substance use; timing of initiation (pre- versus post- scan), duration or frequency of use), or of other possible mediating variables, e.g., tobacco-use, alcohol use, IQ, trauma histories, depressive symptoms (Elsey et al., 2015; Ketcherside and Filbey, 2015). As noted above, this limitation should be considered within the context of the uniqueness of the study sample.

While none of the participants included in this study met criteria for any Axis-I disorders, we cannot rule out the possibility that some of our between-group differences may be related to vulnerabilities for disorders other than substance-use. In addition, as this study did not include any genetic measures, we cannot rule out the possibility that observed between-group differences in neural activity might be related to differences in genetic risk for substance-use and related disorders (Feldstein Ewing et al., 2012; Paloyelis et al., 2012; Jentsch et al., 2014).

4.7. Conclusions and future directions

This study provides preliminary evidence of neural functional alterations within cortico-striato-limbic neurocircuitry among adolescents with and without PCE who experiment with illicit drugs. Given the young age (mean ~ 15 years) and relatively limited drug use by adolescents in this study (none met criteria for abuse or dependence and only half of the adolescents with illicit-substance use had already initiated use at the time of scanning), the observed alterations likely relate to vulnerabilities for, rather than consequences of, illicit-substance use.

Consistent with findings from studies of adults with cocaine dependence, between-group differences varied across cue-conditions (Potenza et al., 2012). Specifically, amongst PCE versus NDE adolescents, illicit-substance use was associated with: (a) increased cortical (OFC, IFG) activity and decreased subcortical activity (cerebellum, parahippocampal gyrus) in response to appetitive cues; (b) decreased cortical and subcortical activity (OFC, PFC, amygdala, hippocampus, brainstem) in response to stressful cues; and (c) decreased cortical activity (DLPFC, PFC) and increased subcortical activity (thalamus, brainstem, putamen) in response neutral/relaxing cues. These data suggest that illicit-substance use among PCE

adolescents is associated with increased subcortical activity in the absence of an overt negative or positive stimulus (neutral/relaxing condition) but with decreased subcortical activity in response to positive (appetitive) and negative (stressful) cues.

Further research is needed to determine the direct clinical implications of these findings, however it is possible that interventions hypothesized to engage ‘bottom-up’ subcortical neurocircuitry, e.g., contingency management (Bickel et al., 2010; Martinez et al., 2011), may be efficacious in reducing illicit-substance use among PCE adolescents. A critical next step will be the assessment of neural response to appetitive drug-related (rather than food-related) cues in this population. Such research is needed to determine the specificity of these findings and will allow for more direct comparison with adult studies (Potenza et al., 2012).

While experimentation with drugs of abuse was relatively common in the overall sample, none of the adolescents in this study met criteria for substance abuse or dependence; thus, the extent to which the observed alterations in BOLD signal relate to more severe patterns of use (e.g., dependence) also remains to be determined. Given the dynamic neurodevelopmental trajectory of cortical and subcortical regions during childhood, adolescence and early adulthood (Giedd, 2004; Gogtay and Thompson, 2010; Casey, 2014; Casey et al., 2014; Raznahan et al., 2014), follow-up scanning of this and other cohorts is needed to characterize functional neurodevelopment over time among adolescents with and without PCE in relation to illicit-substance use initiation and other risk behaviors, as this may help identify critical periods for interventions (Casey et al., 2014).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Role of funding source: This study was supported by the National Institutes of Health; Contrast grant numbers: P50 DA016556, P50 DA09241, UL1-DE19586, RL1 AA017539, R01 DA006025, R01 DA017863, K05 DA020091; T32 DA007238; CASAColumbia; Contract grant sponsor: the Office of Research on Women’s Health, the NIH Roadmap for Medical Research/Common Fund.

References

- Andersen SL, Teicher MH. Stress, sensitive periods and maturational events in adolescent depression. *Trends Neurosci.* 2008; 31:183–191. [PubMed: 18329735]
- Bickel W, Jones B, Landes R, Christensen D, Jackson L, Mancino M. Hypothetical intertemporal choice and real economic behavior: delay discounting predicts voucher redemptions during contingency-management procedures. *Exp Clin Psychopharmacol.* 2010; 18:546–552. [PubMed: 21186929]
- Casey BJ. Beyond simple models of self-control to circuit-based accounts of adolescent behavior. *Annu Rev Psychol.* 2014; 66:295–315. [PubMed: 25089362]
- Casey BJ, Oliveri ME, Insel T. A neurodevelopmental perspective on The Research Domain Criteria (RDoC) Framework. *Biol Psychiatry.* 2014; 76:350–353. [PubMed: 25103538]
- Chambers RA, Taylor JR, Potenza MN. Developmental neurocircuitry of motivation in adolescence: a critical period of addiction vulnerability. *Am J Psychiatry.* 2003; 160:1041–1052. [PubMed: 12777258]

- Chaplin TM, Freiburger MB, Mayes LC, Sinha R. Prenatal cocaine exposure, gender, and adolescent stress response: a prospective longitudinal study. *Neurotoxicol Teratol.* 2010; 32:595–604. [PubMed: 20826209]
- Chung T, Clark DB. Insula white matter volume linked to binge drinking frequency through enhancement motives in treated adolescents. *Alcohol Clin Exp Res.* 2014; 38:1932–1940. [PubMed: 24930680]
- Cisler JM, Elton A, Kennedy AP, Young J, Smitherman S, Andrew James G, Kilts CD. Altered functional connectivity of the insular cortex across prefrontal networks in cocaine addiction. *Psychiatry Res.* 2013; 213:39–46. [PubMed: 23684980]
- Crone EA, Richard Ridderinkhof K, Worm M, Somsen RJM, Van Der Molen MW. Switching between spatial stimulus–response mappings: a developmental study of cognitive flexibility. *Dev Sci.* 2004; 7:443–455. [PubMed: 15484593]
- Delaney-Black V, Chiodo LM, Hannigan JH, Greenwald MK, Janisse J, Patterson G, Huestis MA, Partridge RT, Ager J, Sokol RJ. Prenatal and postnatal cocaine exposure predict teen cocaine use. *Neurotoxicol Teratol.* 2011; 33:110–119. [PubMed: 20609384]
- Devito EE, Meda SA, Jiantonio R, Potenza MN, Krystal JH, Pearlson GD. Neural correlates of impulsivity in healthy males and females with family histories of alcoholism. *Neuropsychopharmacol.* 2013; 38:1854–1863.
- Diener C, Kuehner C, Brusniak W, Ubl B, Wessa M, Flor H. A meta-analysis of neurofunctional imaging studies of emotion and cognition in major depression. *NeuroImage.* 2012; 61:677–685. [PubMed: 22521254]
- Elsej J, Coates A, Lacadie CM, McCrory EJ, Sinha R, Mayes LC, Potenza MN. Childhood trauma and neural responses to personalized stress, favorite-food and neutral-relaxing cues in adolescents. *Neuropsychopharmacol.* 2015; 1038/npp.2015.6
- Feldstein Ewing SW, Mead HK, Yezhuvath U, DeWitt S, Hutchison KE, Filbey FM. A preliminary examination of how serotonergic polymorphisms influence brain response following an adolescent cannabis intervention. *Psychiatry Res Neuroimaging.* 2012; 204:112–116. [PubMed: 23217578]
- Garavan H, Pankiewicz J, Bloom A, Cho JK, Sperry L, Ross TJ, Salmeron BJ, Risinger R, Kelley D, Stein EA. Cue-induced cocaine craving: neuroanatomical specificity for drug users and drug stimuli. *Am J Psychiatry.* 2000; 157:1789–1798. [PubMed: 11058476]
- Giedd JN. Structural magnetic resonance imaging of the adolescent brain. *Ann N Y Acad Sci.* 2004; 1021:77–85. [PubMed: 15251877]
- Glatt SJ, Bolaños CA, Trksak GH, Jackson D. Effects of prenatal cocaine exposure on dopamine system development: a meta-analysis. *Neurotoxicol Teratol.* 2000; 22:617–629. [PubMed: 11106856]
- Gogtay N, Thompson PM. Mapping gray matter development: implications for typical development and vulnerability to psychopathology. *Brain Cogn.* 2010; 72:6–15. [PubMed: 19796863]
- Goldin PR, McRae K, Ramel W, Gross JJ. The neural bases of emotion regulation: reappraisal and suppression of negative emotion. *Biol, Psychiatry.* 2008; 63:577–586. [PubMed: 17888411]
- Goldstein RZ, Volkow ND. Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. *Nat Rev Neurosci.* 2011; 12:652–669. [PubMed: 22011681]
- Hamann S, Canli T. Individual differences in emotional processing. *Curr Opin Neurobio.* 2004; 14:233–238.
- Harle KM, Shenoy P, Stewart JL, Tapert SF, Yu AJ, Paulus MP. Altered neural processing of the need to stop in young adults at risk for stimulant dependence. *J Neurosci.* 2014; 34:4567–4580. [PubMed: 24672002]
- Harvey J, Romano A, Gabriel M, Simansky K, Du W, Aloyo V, Friedman E. Effects of prenatal exposure to cocaine on the developing brain: anatomical, chemical, physiological and behavioral consequences. *Neurotox Res.* 2001; 3:117–143. [PubMed: 15111265]
- Harvey JA. Cocaine effects on the developing brain: current status. *Neurosci Biobehav Rev.* 2004; 27:751–764. [PubMed: 15019425]
- Hommer RE, Seo D, Lacadie CM, Chaplin TM, Mayes LC, Sinha R, Potenza MN. Neural correlates of stress and favorite-food cue exposure in adolescents: a functional magnetic resonance imaging study. *Hum Brain Mapp.* 2012; 34:2561–2573. [PubMed: 22504779]

- Jastreboff AM, Sinha R, Lacadie C, Small DM, Sherwin RS, Potenza MN. Neural correlates of stress- and food cue-induced food craving in obesity: association with insulin levels. *Diabetes Care*. 2013; 36:394–402. [PubMed: 23069840]
- Jentsch JD, Ashenhurst JR, Cervantes MC, Groman SM, James AS, Pennington ZT. Dissecting impulsivity and its relationships to drug addictions. *Ann N Y Acad Sci*. 2014; 1327:1–26. [PubMed: 24654857]
- Kaufman, ASNLK. Administration and Scoring Manual. American Guidance Service, Inc; Circle Pines, MN: 1983. Kaufman Assessment Battery for Children.
- Ketcherside A, Filbey FM. Mediating processes between stress and problematic marijuana use. *Addict Behav*. 2015; 45:113–118. [PubMed: 25661989]
- Kilts C, Gross RE, Ely TD, Drexler KP. The neural correlates of cue-induced craving in cocaine-dependent women. *Am J Psychiatry*. 2004; 161:233–241. [PubMed: 14754771]
- Kilts C, Schweitzer JB, Quinn CK, Gross RE, Faber TL, Muhammad F, Ely TD, Hoffmann JM, Drexler KPG. Neural activity related to drug craving in cocaine addiction. *Arch Gen Psychiatry*. 2001; 58:334–341. [PubMed: 11296093]
- London E, Ernst M, Grant S, Bonson K, Weinstein A. Orbitofrontal cortex and human drug abuse: functional imaging. *Cereb Cortex*. 2000; 10:334–342. [PubMed: 10731228]
- MacDonald AI, Cohen JD, Stenger VA, Carter CS. Dissociating the role of the dorsolateral prefrontal cortex and anterior cingulate cortex in cognitive control. *Science*. 2000; 288:1835–1838. [PubMed: 10846167]
- Malanga CJ, Riday TT, Carlezon WA Jr, Kosofsky BE. Prenatal exposure to cocaine increases the rewarding potency of cocaine and selective dopaminergic agonists in adult mice. *Biol Psychiatry*. 2008; 63:214–221. [PubMed: 17568568]
- Martinez D, Carpenter K, Liu F, Slifstein M, Broft A, Friedman A, Kumar D, Van Heertum R, Kleber H, Nunes E. Imaging dopamine transmission in cocaine dependence: link between neurochemistry and response to treatment. *Am J Psychiatry*. 2011; 168:634–641. [PubMed: 21406463]
- Mayes L, Molfese D, Key A, Hunter N. Event-related potentials in cocaine-exposed children during a Stroop task. *Neurotoxicol Teratol*. 2005; 27:797–813. [PubMed: 16111858]
- McCarthy DM, Bhide PG. Prenatal cocaine exposure decreases parvalbumin-immunoreactive neurons and GABA-to-projection neuron ratio in the medial prefrontal cortex. *Dev Neurosci*. 2012; 34:174–183. [PubMed: 22572769]
- McHugh MJ, Demers CH, Braud J, Briggs R, Adinoff B, Stein EA. Striatal-insula circuits in cocaine addiction: implications for impulsivity and relapse risk. *Am J Drug Alcohol Abuse*. 2013; 39:424–432. [PubMed: 24200212]
- Naqvi NH, Gaznick N, Tranel D, Bechara A. The insula: a critical neural substrate for craving and drug seeking under conflict and risk. *Ann N Y Acad Sci*. 2014; 1316:53–70. [PubMed: 24690001]
- Paloyelis Y, Mehta MA, Faraone SV, Asherson P, Kuntsi J. Striatal sensitivity during reward processing in attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 2012; 51:722–732. e729. [PubMed: 22721595]
- Patel KT, Stevens MC, Meda SA, Muska C, Thomas AD, Potenza MN, Pearson GD. Robust changes in reward circuitry during reward loss in current and former cocaine users during performance of a monetary incentive delay task. *Biol Psychiatry*. 2013; 74:529–537. [PubMed: 23778289]
- Paulus MP, Stewart JL. Interoception and drug addiction. *Neuropharmacology*. 2014; 76(Pt. B):342–350. [PubMed: 23855999]
- Potenza MN, Hong K, Lacadie CM, Fulbright RK, Tuit KL, Sinha R. Neural correlates of stress-induced and cue-induced drug craving: influences of sex and cocaine dependence. *Am J Psychiatry*. 2012; 169:406–414. [PubMed: 22294257]
- Rando K, Chaplin TM, Potenza MN, Mayes L, Sinha R. Prenatal cocaine exposure and gray matter volume in adolescent boys and girls: relationship to substance use initiation. *Biol Psychiatry*. 2013; 74:482–489. [PubMed: 23751204]
- Raznahan A, Shaw PW, Lerch JP, Clasen LS, Greenstein D, Berman R, Pipitone J, Chakravarty MM, Giedd JN. Longitudinal four-dimensional mapping of subcortical anatomy in human development. *Proc Natl Acad Sci U S A*. 2014; 111:1592–1597. [PubMed: 24474784]

- Richardson GA, Larkby C, Goldschmidt L, Day NL. Adolescent initiation of drug use: effects of prenatal cocaine exposure. *J Am Acad Child Adolesc Psychiatry*. 2013; 52:37–46. [PubMed: 23265632]
- Shaffer D, Fisher P, Lucas CP, Dulcan MK, Schwab-Stone ME. NIMH Diagnostic Interview Schedule for Children Version IV (NIMH DISC-IV): description, differences from previous versions, and reliability of some common diagnoses. *J Am Acad Child Adolesc Psychiatry*. 2000; 39:28–38. [PubMed: 10638065]
- Sinha R. Modeling stress and drug craving in the laboratory: implications for addiction treatment development. *Addict Biol*. 2009; 14:84–98. [PubMed: 18945295]
- Sinha R, Lacadie C, Skudlarski P, Fulbright RK, Rounsaville BJ, Kosten TR, Wexler BE. Neural activity associated with stress-induced cocaine craving: a functional magnetic imaging study. *Psychopharmacol*. 2005; 183:171–180.
- Stanwood GD, Washington RA, Levitt P. Identification of a sensitive period of prenatal cocaine exposure that alters the development of the anterior cingulate cortex. *Cereb Cortex*. 2001a; 11:430–440. [PubMed: 11313295]
- Stanwood GD, Washington RA, Shumsky JS, Levitt P. Prenatal cocaine exposure produces consistent developmental alterations in dopamine-rich regions of the cerebral cortex. *Neurosci*. 2001b; 106:5–14.
- Stewart JL, Flagan TM, May AC, Reske M, Simmons AN, Paulus MP. Young adults at risk for stimulant dependence show reward dysfunction during reinforcement-based decision making. *Biol Psychiatry*. 2013; 73:235–241. [PubMed: 23021534]
- Wahlstrom D, White T, Luciana M. Neurobehavioral evidence for changes in dopamine system activity during adolescence. *Neurosci Biobehav Rev*. 2010; 34:631–648. [PubMed: 20026110]
- Wang W, Nitulescu I, Lewis JS, Lemos JC, Bamford IJ, Posielski NM, Storey GP, Phillips PEM, Bamford NS. Overinhibition of corticostriatal activity following prenatal cocaine exposure. *Ann Neurol*. 2013; 73:355–369. [PubMed: 23225132]
- Wolf OT. Stress and memory in humans: twelve years of progress? *Brain Res*. 2009; 1293:142–154. [PubMed: 19376098]
- Yip S, Potenza E, Balodis IM, Lacadie C, Sinha R, Mayes L, Potenza MN. Prenatal cocaine exposure and adolescent neural responses to appetitive and stressful stimuli. *Neuropsychopharmacol*. 2014; 39:2824–2834.
- Yip S, Worhunsky PD, Rogers RD, Goodwin GM. Hypoactivation of the ventral and dorsal striatum during reward and loss anticipation in antipsychotic and mood stabilizer-naïve bipolar disorder. *Neuropsychopharmacol*. 2015; 40:658–666.

- Prenatal cocaine exposure (PCE) is associated with increased rates of illicit-substance use
- Main and interactive effects of illicit-substance use on neural responses assessed in a sample of 68 adolescents with and without PCE
- Findings suggest different neural substrates of illicit-substance use between adolescents with and without *in utero* cocaine exposure

Figure 1. Three-way interaction of illicit-substance use initiation (yes/no), prenatal cocaine exposure (yes/no) and cue condition (favorite food/stress/neutral-relaxing) on BOLD responses (pFWE<.05)

Panel 1 A shows whole-brain findings for the three-way interaction of illicit-substance use initiation (yes/no), prenatal cocaine exposure (yes/no) and cue condition (favorite food/stress/neutral-relaxing) on BOLD response (pFWE<.05). For illustrative purposes average BOLD signal ($\pm$ standard error) is plotted below (Panel 1B) for each cue-condition for each participant group. R=Right; L=Left

Figure 2.

Associations of illicit-substance use initiation among PCE versus NDE adolescents during exposure to favorite-food, stressful and neutral-relaxing cues ($p_{FWE} < .05$).

Comparisons of neural activations amongst PCE versus NDE adolescents in relation to illicit-substance use were conducted using a 'double-contrast' of PCE adolescents (illicit-substance users – illicit-substance non-users) versus NDE adolescents (illicit-substance users – illicit-substance non-users) during the different cue conditions.

Red-yellow indicates PCE illicit-substance users – illicit-substance non-users > NDE illicit-substance users – illicit-substance non-users.

Blue-purple indicates PCE illicit-substance users – illicit-substance non-users < NDE illicit-substance users – illicit-substance non-users.

Selected brain regions highlighted for emphasis using white overlays. For further details, please refer to the Supplemental Materials (Tables 4–6).

PCE= prenatal cocaine exposure; NDE=no prenatal drug-exposure; R=right; L=left; mPFC=medial prefrontal cortex; OFC=orbitofrontal cortex

Figure 3.

Correlations between brain activations and subjective ratings of anxiety and food craving during exposure to stressful, favorite-food and neutral-relaxing cues among adolescents with and without lifetime illicit-substance use initiation

A. Whole-brain correlations between subjective ratings and brain activity among adolescents with lifetime illicit-substance use initiation. Selected brain regions highlighted for emphasis using white overlays. For further details, please refer to the Supplemental Materials (Table 7).

B. Individual participants' average signal from selected subclusters are plotted against individual participants' subjective ratings.

R=Right; L=Left; Acc=Anterior cingulate; mPFC=medial prefrontal cortex; NDE= non-prenatally-drug-exposed; PCE=prenatal cocaine exposure

Demographic and clinical characteristics and illicit-substance-use status among prenatally cocaine exposed (PCE) and non-prenatally-drug exposed (NDE) adolescents

Table 1

	NDE (n=22)		PCE (n=46)		Analysis statistics		
	Mean	SD	Mean	SD	F	df	p
Age ^a	14.50	0.60	14.91	1.03	3.04	67	0.09
BMI	25.95	6.52	23.24	4.96	3.62	67	0.06
IQ ^b	99.05	15.39	91.39	12.16	4.47	60	0.04
CTQ ^c	31.90	7.79	37.39	10.40	4.42	63	0.04
	n	%	n	%	χ^2	df	p
Gender (male)	14	63.6	27	58.7	0.15	1	0.70
Hispanic	5	22.7	4	8.7	2.55	1	0.11
Race					5.29	3	0.15
African American	14	63.6	39	84.8			
Caucasian	5	22.7	4	6.1			
Biracial	3	13.6	2	4.3			
Native American	0	0.0	1	2.2			
Lifetime tobacco use	7	31.8	29	63.0	5.84	1	0.02
Lifetime alcohol use	12	54.5	38	82.6	6.02	1	0.01
Any lifetime illicit use ^d	10	45.5	39	84.8	11.43	1	<.01
Timing of lifetime illicit use					1.81	1	0.18
Pre-scan initiation	3	30.0	21	53.8			
Post-scan initiation	7	70.0	18	46.2			
Past 30-day illicit use	1	5.2	15	32.6	6.51	1	0.01

SD = standard deviation; df = degrees of freedom; BMI = body mass index; CTQ= Childhood Trauma Questionnaire

^a age at time of MRI scanning

^b IQ data missing for seven participants (two NDE, five PCE)

^c CTQ data missing for four participants (two NDE, two PCE)

^d Illicit use includes any cannabis, cocaine, opiates, crystal meth, PCP, ecstasy or inhalant use; assessed via self-report and urinalysis

Table 2

Main effects of lifetime illicit substance-use (yes/no) and cue condition (favorite food / stress / neutral-relaxing) on brain activations (pFWE<05)

Cluster description	Peak				
	BA	x	Y	z	mm ³
Main effect of lifetime illicit-substance use					
L Acc / thalamus / IFG / insula / parahippocampal gyrus / MFG / premotor cortex / SMA / hippocampus	6, 44	-31	-42	4	15619
R thalamus / caudate / cingulum / Pcc / precentral gyrus / postcentral gyrus / IFG / DLPFC / premotor cortex / SMA / middle temporal gyrus / angular gyrus	6, 9, 31, 39	34	-60	27	22047
Main effect of cue condition					
Primary sensory area / primary motor area / premotor cortex / SMA / Acc / caudate / thalamus / insula / brainstem / superior temporal gyrus / temporal pole / supramarginal gyrus	6, 22, 38, 40	6	4	39	94648
L temporal lobe/ fusiform gyrus / angular gyrus / middle temporal gyrus / superior temporal gyrus	21, 22, 39	-50	-22	-4	12731
L insula / superior temporal gyrus / premotor cortex / SMA	6, 22	-35	9	8	7187
L supramarginal gyrus / Primary Motor area / primary sensory / somatosensory association area / associative visual	7, 19, 40	-18	-50	56	16911

There was no significant main effect of PCE status. L=left; R=right; Acc=anterior cingulate cortex; IFG=inferior frontal gyrus; MFG=medial frontal gyrus; SMA=supplementary motor area; Pcc=posterior cingulate cortex; DLPFC=dorsolateral prefrontal cortex

Table 3

Three- and two-way Interaction effects of lifetime illicit-substance use (yes/no), prenatal cocaine exposure (yes/no) and cue condition (favorite food / stress / neutral-relaxing) on BOLD response (pFWE<.05)

Cluster description	Peak			F-statistic		
	x	y	z	peak	mean	SD
Three-way interaction between cue condition, lifetime illicit-substance use and prenatal cocaine exposure						
L postcentral gyrus / supramarginal gyrus / precentral gyrus / inferior parietal lobule / fusiform gyrus / inferior temporal gyrus / L insula	-63	-15	24	10.26	4.27	1.15
R insula / postcentral gyrus / superior temporal gyrus / supramarginal gyrus	58	-17	25	7.85	3.92	0.73
Two-way interactions:						
<i>Condition and prenatal cocaine exposure</i>						
R cuneus / primary visual / secondary visual / Pcc / lingual gyrus	-11	-95	0	10.13	4.33	1.10
Premotor cortex / SMA / superior frontal gyrus / middle frontal gyrus	-5	14	62	7.37	3.93	0.72
<i>Lifetime illicit-substance use and prenatal cocaine exposure</i>						
R middle occipital gyrus / associative visual	34	-87	9	15.16	6.22	1.90

There was no significant two-way interaction between condition and illicit-substance use.

L=left; R=right; SMA=supplementary motor area; Pcc=posterior cingulate cortex