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

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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.
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 multilevel ANOVAs (pFWE< .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.

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

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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 and Canli, 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 were 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 (Elsey 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 2[1].

2.3. Imagery script development and scanning procedures

During fMRI scanning, adolescents were presented with six personalized 2.5-min 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-min baseline period and followed by a 1-min quiet recovery period and a progressive relaxation period (approximately 2 min). In order to ensure that there were no residual effects of the previous script on each subsequent script, new trials were initiated 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 Fig. 1[2].

[1] Supplementary material can be found by accessing the online version of this paper at http://dx.doi.org and by entering doi: 10.1016/j.drugalcdep.2015.11.012.

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